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EPHEDRINE AND RELATED SUBSTANCES

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I. INTRODUCTION

The rise of ephedrine from obscurity to its present state of widespread popularity, within less than five years, involves a variety of features of unusual interest. Much of the initial enthusiasm for the drug was doubtless due to the somewhat dramatic circumstance that the traditional faith of the Chinese in one of their ancient remedies was about to be justified by Western science. While ephedrine has recently found a real place in therapeutics, the drug was known to experimenters and clinicians for some thirty years before its possibilities were appreciated. The reason for this tardy recognition was simply the failure of the original investigators to use any but toxic doses in their animal experiments—a circumstance which illustrates the readiness with which an initial misconception may be propagated and may influence the subsequent fate of a new remedy. The history of ephedrine is therefore of more than usual interest.

Apart from the historical aspect, ephedrine has been the object of a great deal of investigation on the part of laboratory workers and clinicians. The result has been not only the discovery of unanticipated uses for the drug but—of greater ultimate importance—a renewal of interest in the problem of the relation of chemical composition to physiological actions, and the direction of attention to the incompleteness of our knowledge concerning the mode of action of sympathomimetic drugs (i.e., those which produce effects similar to the result of excitation of sympathetic innervations). It is now quite certain that ephedrine, in spite of its present popularity, is far from ideal in certain respects. In the search for other remedies of this sort important progress has already been made, and undoubtedly much more lies in the immediate future. For the benefit of those concerned in such work, and of the clinicians in whose hands rests the final decision concerning the validity of laboratory experimentation with agents of possible therapeutic importance, a compilation of the literature dealing with ephedrine should serve a useful purpose. For if ephedrine is not the only agent of this sort to have been introduced into therapeutics since epinephrine was discovered, it has certainly been the object of more investigation than any other. In spite of this, the literature is full of disagreements and unjustified assumptions with respect to the fundamental features in the action of the drug, though the clinical results are quite uniform in indicating that it produces effects that are of the same nature as those of epinephrine. It is inevitable that workers with other substances of this sort will be confronted with the same difficulties. These can be obviated, to some extent at least, if it is generally realized that a drug can be sympathomimetic, in the original sense of the term, without duplicating all of the effects of epinephrine.

HISTORICAL

As is generally known, ephedrine is an alkaloidal active principle obtained from a Chinese herb which, under the name of Ma Huang, has been used by native physicians for some 5000 years. It was one of the drugs which is said to have been tasted by the Emperor Shen Nung, who placed it in the "medium class." It is mentioned in the Pentsao Kang Mu, the Chinese dispensatory, written in 1596 by Shih-Cheng Li. According to this authority Ma Huang is of value as a circulatory stimulant, diaphoretic, antipyretic, sedative in cough, and it is an ingredient of many famous prescriptions. An English translation of the ancient Chinese records can be found in the paper by Hagerty and Woo.

Plants similar to, if not identical with Ma Huang have been employed as medicines since remote antiquity in other parts of the world. Thus, it is said (Berendes) that Greek physicians employed plants of the same genus (*Ephedra*) as Ma Huang, and that the Hippuris of Dioscorides (about 50 A.D.) was *E. fragilis* var. *graeca*. The top of this plant was used as an astringent; taken with wine it was said to produce diuresis and to cure dysentery, and both root and top were reputed to be useful in the treatment of cough, orthopnea, and internal rupture (Berendes).

In Russia *Ephedras* have been in medical use since olden times. In the 19th century decoctions of *E. vulgaris*, together with milk and butter, were recommended in the treatment of rheumatism and were regarded as a specific remedy for syphilis and gout, the latter virtue being attributed to the twigs and roots of the plant. The sap and candied fruits were used in the treatment of respiratory disorders. A peasant named Kusmitsch effected such marvelous cures with decoctions of *Ephedra* that he won a wide reputation, and Bechtin (1891) reported very striking results with decoctions of *E. vulgaris* in patients with rheumatism. Sassetsky and Lewaschew, however, were unable to confirm these results (Grahe).

In India the dried branches of *E. pachyclada*, or *E. intermedia*, are thought to possess medicinal value, but they are chiefly used in religious (Parsi) ceremonials. It is also said that this plant, mixed with milk and honey and allowed to ferment, was the "soma" of the Vedas, which was used to induce an exhilarating intoxication. Incidentally, this appears to be the only instance of employment of an *Ephedra* for the purpose of pleasurable intoxication, and it is possible that the effects were due to alcohol in this case.

In America a number of *Ephedra* plants were used by the Indians for various purposes. *E. antisyphilitica*, *E. californica*, and *E. nevadensis* were regarded as valuable in the treatment of syphilis and gonorrhoea, and were used as local applications as well as by internal administration. The Coahuila Indians made a cooling beverage from *E. nevadensis*, and the Panamint Indians made bread from the ground roasted seeds of the same plant. The Indians and Spaniards used decoctions of *E. californica* as a tonic and blood purifier, and *E. trifurca* was regarded as an excellent remedy for nephritis. In Mexico, *E. aspera* is still used occasionally in the treatment of pneumonia, and in Zacatecas *E. pedunculata* is highly esteemed as a remedy for pleurisy and pneumonia.

It appears, therefore, that the *Ephedras* have long been utilized as empirical remedies in many discontiguous parts of the world. On the whole, they seem to have enjoyed a reputation for two different sorts of usefulness—first, in the treatment of venereal diseases, and second, in treating disorders of the respiratory system.

The development of a useful modern drug out of these ancient remedies has centered upon the Chinese plant Ma Huang and, as is usually the case, has followed as a natural consequence of the isolation of an active principle. Pioneer work along these lines was done wholly by the Japanese, whose interest in Chinese drugs was naturally greater than that of the Western world because most of their empirical materia medica—including Ma Huang—was derived from the ancient culture of China. An active principle was first isolated from Ma Huang in 1885 by G. Yamanashi, who obtained a crystalline though impure substance. After his death the study was continued by Nagai, with the assistance of Y. Hori, who obtained the alkaloid in pure form (1887). The same compound was obtained in Germany by E. Merck in 1888. The name ephedrine was first applied to this substance by

Nagai, though the name had already been coined in 1875 by Loew for the tannin which he had prepared from *E. antisyphilitica*. The name ephedrine is now used only in the sense in which Nagai employed it, viz., to designate an alkaloidal active principle of Ma Huang and other *Ephedras*.

Nagai's ephedrine was subjected to physiological investigations by Miura (1887). This study disclosed the toxic effects of large doses upon the circulation and demonstrated the mydriatic action of the drug. As a result it was introduced to Western medicine as a new mydriatic, but its vogue was limited and brief. Apparently it was not utilized for other purposes and was regarded as a very toxic substance. It is interesting to note that ephedrine, which has recently attained popularity as a substitute for or adjuvant to epinephrine, was available in pure form five years before the actions of suprarenal extracts were first worked out completely and more than twelve years before epinephrine, the active principle of suprarenal medulla, was first isolated.

Subsequently interest in ephedrine was, for many years, almost wholly limited to analyses of its chemical composition and to attempts at synthesizing it (see below). Six years before our work was undertaken the Japanese investigators Amatsu and Kubota (1917) demonstrated the essentially sympathomimetic (epinephrine-like) effects of ephedrine, and other workers—Hirose, and To—also contributed to the same conclusion. These publications attracted little attention in America and Europe, but as a result of their work the Japanese became so convinced of the value of ephedrine in the treatment of one condition that is relieved by epinephrine—namely, asthma—that an ephedrine-containing preparation was put on the market in Mukden under the name of Asthmatol. No publication was made of the results obtained with this product and when the question of the therapeutic possibilities of ephedrine was reopened in 1923 this development was unknown to the Western world (and to the authors). It is proper, however, that the Japanese scientists should be given due credit for having been the first to appreciate the usefulness of ephedrine for purposes other than ophthalmologic.

The work done by the authors upon this subject was the result of a suggestion made by a Chinese druggist, in response to an inquiry concerning native drugs which might be expected to possess real actions. Among others, Ma Huang was mentioned, and a small supply was obtained for future investigation. In the autumn of 1923 a decoction made from this material was injected into a vein of an anesthetized dog remaining alive at the end of a student exercise. The consequent circulatory effect was the one now familiar as that of ephedrine, and attention was concentrated upon this promising drug. A crystalline alkaloid was readily isolated from it, and further experiments demonstrated that this was the active principle, that it possessed epinephrine-like effects, that it was of comparatively low toxicity, and that it was effectively absorbed from the gastro-intestinal tracts of dogs and men. A search of the literature disclosed the identity of this substance as ephedrine. Clinical trial of the drug was limited by the small quantity of ephedrine available at the time. As soon as a sufficient supply was prepared it was submitted to Dr. T. G. Miller, of the University of Pennsylvania, and to Dr. L. G. Rowntree, of the Mayo Clinic, for clinical experiments. The results being favorable, ephedrine was made available to clinicians in general, as rapidly as possible. In 1926 ephedrine was submitted to the Council of Pharmacy and Chemistry of the American Medical Association, and was subsequently approved by it. The drug is now prepared by a number of manufacturers and is quite generally obtainable.

One of the interesting aspects of the usefulness of ephedrine, as established by modern clinicians and experimenters, is that it justifies the Chinese tradition concerning Ma Huang in many respects.

II. PHARMACOGNOSY AND CHEMISTRY

1. Botany

Ephedrine occurs in certain plants of the genus *Ephedra* (family Ephedraceae) which includes a large number of species (35, according to Engler and Prantl, 1926; 45, according to the Index Kewensis, 1895–1920). These are distributed throughout the temperate and subtropical regions of Europe, Asia, and America. They are found in an area extending from the middle Amur region through central Asia, including its deserts and covering China and Arabia, to the Mediterranean and even to the Canary Islands (Engler and Prantl), as well as

Siberia, Hungary, the Carpathian Mountains, the Western Alps, and Western France. In the Americas they grow along the Rocky Mountains as far south as New Mexico, from Bolivia to Patagonia, and from Paraguay to the Atlantic Ocean.

Only a few of these *Ephedras* contain ephedrine. In China ephedrine-bearing plants are found in the Tai-hung Mountains, which are the site of the Great Wall in Chihli Province. They also occur in Shansi, Shensi, Kansu, Honan, and Hupeh Provinces (Read and associates, 1928). They are also found in Northern Chosen (Korea) and in Akita Prefecture in Japan. In India and Tibet they occur along the Himalaya Mountains (Chopra and associates).

The actual identification of Ma Huang has been somewhat uncertain. It was formerly classified as *E. vulgaris* var. *helvetica* (Nagai; Botanical Nomenclature, etc.), but this name appears to be obsolete. Cowdry (1922) identified Ma Huang as *E. equisetina*, and this is the name recognized by the Council on Pharmacy and Chemistry of the American Medical Association for the plant from which ephedrine is obtained. Holmes (1926) suggested that Ma Huang is *E. intermedia* var. *tibetica*, while Stapf (1927) gave a provisional new name of *E. sinica* to specimens submitted by Read and by Parke, Davis & Company. Liu and Read (1929) identified another species, *E. distachya*, which is found in Western Chihli and is also known as Ma Huang. This statement needs confirmation. At present it appears that Ma Huang, from which most of the present supply of ephedrine is obtained, is *E. sinica* or *E. equisetina* (Small and Short). It has been shown recently by Chopra and his coworkers (1928), that ephedrine also occurs in the Indian species, *E. vulgaris*, *E. pachyclada* or *intermedia*, and *E. intermedia* var. *helvetica*. Their results have been confirmed by Read and Feng (1928).

These are the principal natural sources of ephedrine at present, though ephedrine is also found in plants growing in Southern Europe, in Northern China and in Japan. Other *Ephedras* have been examined but they contained no alkaloid, or only the isomeric pseudoephedrine, which is distinctly less useful than ephedrine. The American species *E. trifurca*, *E. nevadensis*, *E. californica*, and *E. viridis* were examined by Nielson, McCausland, and Spruth, and found to contain no alkaloid. Terry obtained the same negative result with *E. nevadensis*. Clark and Groff reported the presence of pressor substances in extracts of *E. californica* and *E. nevadensis,* though no crystalline active substance could be isolated. Their results were not substantiated by De Eds and Butt or by Read and Feng. Black and Kelly found only pseudoephedrine in *E. alata,* collected in Morocco. None of the American *Ephedras* have been shown to contain ephedrine, and upon transplanting the Swiss *E. vulgaris* (*E. distachya*), which is believed to yield ephedrine, to this country, no alkaloid was found in it after the first year of growth (Nielson and McCausland, 1928).

2. *Properties of ephedrine*

a. Isolation. Ephedrine, having the solubility reactions of a typical alkaloid, is very easily separated from an extract of the plant. The following procedure has been found satisfactory.

The powdered crude drug is extracted with 60 per cent alcohol, the extract concentrated and treated with strong ammonum hydroxide or sodium carbonate. This causes precipitation, and filtration is necessary: ephedrine is present in both precipitate and filtrate, so that both must be dealt with. The akaloid is extracted from them by means of chloroform or ether. Upon removal of the solvent the residue is neutralized with dilute HCl or H_2SO_4, thus forming the corresponding salt of the alkaloid, which is finally purified and repeatedly crystallized from absolute alcohol. It is obvious that a chemical assay of ephedra-bearing plants is readily carried out, and this is fortunate because no satisfactory bio-assay has been developed.

b. Yield. Different investigators have obtained widely divergent results, even with the same plant, as shown in table 1. Generally speaking, the earlier workers obtained lower yields than the more recent ones, most of whom have succeeded in isolating more than 1 per cent of total alkaloids from the Chinese plants: of this 80 per cent or more is ephedrine. The Indian species *E. pachyclada* and *E. intermedia* var. *tibetica* have a distinctly lower ephedrine content than the Chinese.

Read and his associates in Peiping have made careful studies of this question. They (Feng and Read) find that the low yield of ephedrine obtained by previous workers was due to incomplete alkalinization of the percolate before extraction with chloroform or ether, and emphasize the necessity of adding a large excess of ammonium hydroxide in order to liberate the alkaloids completely. They have also studied the variations in yield of ephedrine from different parts of the plant and at different seasons of the year (Feng and Read, 1928). They find progressive increase in total ephedrine content from spring to autumn, the maximum being attained just before the frosts. The old Chinese custom of collecting the plant in the autumn therefore appears to be based upon sound observation. During the flowering season the male plant contains more alkaloid than the female, the difference being greatest in May. After the fruiting season the alkaloid content is practically equal in plants of both sexes. With respect to the distribution of alkaloid in different parts of the plant, these investigators find (in *E. equisetina*) that the nodes contain much less ephedrine than the internodes, and that the root, berries, seeds, and woody stalks contain none at all. Similar conclusions were reached by Chopra and his associates with respect to Indian species of *Ephedra.*

TABLE 1

Assay of Ephedras reported by different workers

SPECIES	TOTAL ALKALOIDS, PER CENT OF CRUDE DRUG	EPHEDRINE, PER CENT OF THE TOTAL	AUTHOR
Ma Huang	0.31–0.40		Nagai
Ma Huang	0.02–0.09		Chen
Ma Huang	0.30		Masucci and Suto
Ma Huang	0.40–0.86		Schoetzon and Needham
Ma Huang	0.20–0.90		Neilson, McCausland and Sprunt
Ma Huang	0.64–1.43		Williams
E. Equisetina	1.75	85–90	Feng and Read
B. Sinica	1.32	80–85	Feng and Read
E. vulgaris	1.02–1.27	50	Chopra, Dikshit and Pillai
E. vulgaris	1.65–1.70	70–80	Read and Feng
E pachyclada	1.8	30–36	Chopra, Dikshit and Pillai
E. pachyclada	1.15	30–40	Read and Feng
E. intermedia var. *Tibetica*	0.25–0.60		Chopra, Dikshit and Pillai

The special tissue of the plant stem which is concerned in manufacturing or storing ephedrine has not been determined. Nothing is known about the manner in which it is synthesized by the plant or the circumstances under which it may be transformed into its optical isomer, pseudoephedrine, or demethylated or methylated within the plant. A study of the climatic and soil conditions under which the plant would produce its maximum yield of ephedrine could be made with profit.

c. Recent commercial development. The recent popularity of ephedrine has led to the development of a considerable industry in China. Ephedrine has been upon the market for more than 30 years. It has been listed in E. Merck's Index since 1896. Japanese manufacturers (Dainihon Seiyaku Kabushiki Kaisha, of Osaka, later succeeded by the firms of Tanabe and Takeda) also prepared ephedrine, and the proprietary preparation Asthmatol contained ephedrine. As far as is known to the reviewers, these were the only commercial supplies of ephedrine in the world prior to 1924, and the quantities produced were relatively insignificant, since the drug was scarcely used at all except for chemical investigations. According to Mr. G. Woodard, Assistant Trade Commissioner of the United States at Shanghai, Ma Huang was exported almost exclusively through German firms for the past 30 years. Read (1928) states that Ma Huang was probably never exported from Tientsin prior to August, 1926, but from this time the trade developed rapidly. By the end of 1926 the exports from Tientsin alone, and to the United States alone, amounted to 224,058 pounds, valued at $17,753, during 1927 they were 622,060 pounds and $64,840, and for the first 11 months of 1928 they were 1,003,700 pounds and $69,300. (The figures for 1926 and 1927 are cited by Read; those for 1928 were furnished by Mr. A. G. Ward, U. S. Vice-Consul at Tientsin.) In addition to the crude drug, ephedrine hydrochloride, prepared by the Department of Chemical Products of Peiping Union Medical College, was exported through Tientsin as follows: in 1926, 12½ pounds, valued at U. S. $3,612; in 1927, 23 pounds and $7,490; in 1928 (to December 1) 20 pounds and $3,688. Ma Huang has also been exported from Shanghai and Hankow, but the quantities concerned are unknown to the writers: it is certain that the above figures underestimate the Chinese trade in this drug. Furthermore, ephedrine-containing plants are also exported from Osaka and Tokyo, Japan, and from Karachi and Rawalpindi, India. The world supply of these plants appears to have satisfied the demand during 1927, and is now greater, for the average price of Ma Huang shipped from Tientsin to the United States during 1927 was U. S. $10.43 per 100 pounds, while during 1928 it fell to $6.91.

In contrast with the two concerns—one German, one Japanese—who were the sole purveyors of pure ephedrine prior to 1924, the drug is now being prepared by eight firms in the United States, by one in Canada, by three in England, by two in Germany, by three in China, by four Japanese companies, and by two in India. There may be others of which the writers are unaware.

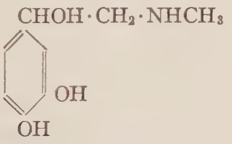
d. Physical and chemical characteristics. The alkaloid ephedrine is deposited from an ether solution as an oily substance, but colorless and odorless crystals appear as needles or rosettes on standing or recrystallization. These melt at 34–40°C. and boil above 200°C. The specific rotation, $[\alpha]_D^{20}$, of the base is between $-6°$ and $-7.5°$. The alkaloid is soluble in ether, chloroform, alcohol, petroleum ether, and water, the solutions being strongly alkaline to litmus paper. The crystallography of ephedrine has been investigated by Schwankte, and Walcott (quoted by Peterson, 1928). Geppert investigated its effects upon the surface tension of water. A peculiar reaction of ephedrine is the formation of the hydrochloride when it is shaken with chloroform: this was pointed out by Peterson (1928), and is responsible for the high melting point incorrectly reported by Chen (1925) for ephedrine base.

For laboratory and clinical uses the hydrochloride and sulphate derivatives are most commonly used. The hydrochloride appears as white odorless crystals, with a melting-point of 214–220°, $[\alpha]_D^{20}$ $-33°$ to $-35.5°$; it contains 17.3 to 17.7 per cent of Cl^-, is soluble in water and alcohol, insoluble in chloroform, ether, and paraffine oil. The sulphate occurs as fine, white, odorless crystals, melting at 240–243°C. $[\alpha]_D^{20}$ $-29°$ to $-30°$, containing 21.8 to 23.1 per cent of $SO_4{}^{--}$, soluble in water and hot alcohol, insoluble in ether, chloroform, and paraffine oil.

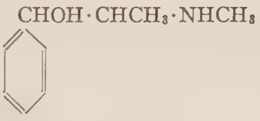
Solutions of ephedrine or its salts react with few of the alkaloidal reagents. With Mayer's reagent there is a turbidity or white precipitate, according to the degree of concentration. Tsiang and Brown (1927) described characteristic micro-crystalline reactions when ephedrine is treated with Millon's reagent, gold chloride, platinic chloride, or Kraut's reagent. The most serviceable qualitative reaction of ephedrine is that with copper sulphate and sodium hydroxide, which was first pointed out by Nagai (1892): a purple color appears, which is extractible with ether. This test is sensitive to one part of ephedrine in 400, and if the concentration exceeds 1 in 40 a pinkish purple precipitate is formed, and this is completely soluble in ether.

The chemical behavior of ephedrine has been exhaustively studied by E. Schmidt, Nagai, E. R. Miller, Flaecher, Calliess, Emde, and others. Probably the most important property is its stability: ephedrine solutions are not decomposed by exposure to light, air, or heat, and age apparently does not affect their activity. Thus, a solution of ephedrine hydrochloride, prepared and sealed in a sterile ampule by the authors on December 23, 1923, showed no change in appearance when opened on March 14, 1929, and produced the customary pressor response when injected into a pithed cat. Kendall and Witzmann (1927) have demonstrated the great resistance of ephedrine to oxidation, as compared with epinephrine: the former is not oxidized by dibromphenolindophenol, naphtholdichlorindophenol, methylene blue, or indigo carmine, while the latter is oxidized by all these agents.

e. Structure and isomerism. The chemical constitution of ephedrine has been studied by Ladenburg and Oelschlägel, Nagai, E. Merck, E. Schmidt, E. R. Miller, Rabe, Ogata, and others. The empirical formula has been definitely established as $C_{10}H_{15}ON$, the structural formula as $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NHCH_3$, or β-phenyl-β-hydroxy-α-methyl-ethyl-methyl amine, or 1-phenyl-2-methylaminopropanol-1, or α-hydroxy-β-methylamino-propyl benzene:



Epinephrine



Ephedrine

Its chemical similarity to epinephrine is obvious.

The above graphic formula of ephedrine contains two asymmetric carbon atoms, so that two sets of stereoisomers, making six in all, are possible. All have been prepared synthetically (see the following section); they are designated *l*-, *d*-, and *dl*-ephedrines, *d*-, *l*-, and *dl*-pseudoephedrines, the *dl* forms being optically inactive racemic mixtures. Only two occur in nature, namely *l*-ephedrine, which is the ephedrine now in use, and *d*-pseudoephedrine, which is also found in Ma Huang, and which is the pseudoephedrine first isolated by Merck from European *Ephedra*, and recently prepared by Chou and Read (1926) from Ma Huang extracts from which ephedrine had been removed. This is the pseudoephedrine of current literature. Pseudoephedrine is quite unlike ephedrine in melting-point (118°C.), optical rotation ($[\alpha]_D^{20} + 50°$) and, to a certain extent, in physiological effects. It is of particular interest, however, because ephedrine can readily be converted into it under certain conditions, which were studied by E. Schmidt, Nagai, and Calliess, more recently by Chou (1926). The literature dealing with the isomerism of these alkaloids was reviewed by Chen and Kao (1926). Emde (1928) has obtained evidence that the —OH and —$NHCH_3$ groups are distant from each other in the ephedrine molecule but close together in the pseudoephedrine molecule.

f. Other alkaloids occurring in Ma Huang. In addition to ephedrine and pseudoephedrine, three other related (but not isomeric) alkaloids have been isolated from Ma Huang. Smith (1927, 1928) obtained *l*-methyl-ephedrine and nor-*d*-pseudoephedrine. Nagai and Kanao (1928) confirmed these findings, and succeeded in isolating a third alkaloid, namely, *d*-methyl-pseudoephedrine. It appears therefore, that ephedrine, like several useful alkaloids, occurs in nature along with closely related substances, though of these only pseudoephedrine occurs in appreciable quantity.

g. Synthesis of ephedrine. E. Schmidt and his associates made various attempts and advances toward the synthesis of ephedrine. Fourneau (1904) prepared a compound having the formula of ephedrine. He and his associates later succeeded in the synthesis by different methods. His process was patented in England (1927). Nagai accomplished the synthesis in 1911 and patented his product in Japan, the United States, Canada and England, under the name of *Methylmydriatine*. All these products were racemic, as is always the case when an optically active substance is synthesized. However, according to Ogata (1919), Nagai succeeded in 1918 in resolving his product into *l*- and *d*-ephedrines. Recently, Nagai (1927) has stated that he was able to synthesize two racemic ephedrines, one melting at 40°, the other at 70°, and in separating each into its *d*- and *l*-components by means of tartaric acid: the pair obtained from the mixture melting at 70° he called isoephedrines (identical with pseudoephedrines). Späth and Göhring (1920) described their complete success in the synthesis and separation of all six isomers. Eberhard (1915) also succeeded in synthesizing racemic ephedrine. Kanao (1927) reported the success of his attempts to synthesize and separate the six isomers, confirming the results of Späth and Göhring. E. Merck has recently placed synthetic racemic ephedrine on the market, under the name of *Ephetonin;* the process of preparation is patented in Germany and England. Manske and Johnson (1929) and Skita and Keil (1929) have recently achieved new syntheses of ephedrine. Fourneau and Nicolitch, Manske and Johnson, and Neuberg, Jacobson and Wagner employed chemical agents other than tartaric acid in the resolution of racemic ephedrine.

It is obvious that the final confirmation of the deduced structure of ephedrine—namely, synthesis of the substance—has been furnished repeatedly. At present the natural product is more widely used than the synthetic and at the time of writing American manufacturers are supplying only natural ephedrine.

III. PHARMACOLOGICAL ACTION

Chen and Schmidt (1924) called the attention of the Western world to ephedrine in the belief that the actions of the drug were essentially sympathomimetic and that it should achieve a usefulness similar to that of epinephrine. This belief has been strengthened by subsequent clinical experience, and appears to be amply justified. However, when the actions of ephedrine are compared with the pattern of sympathomimetic effects—i.e., the actions of epinephrine—in the laboratory, differences are perhaps more frequent than analogies, and there has recently been a tendency on the part of several investigators to emphasize the differences as indicative of an absence of any sympathomimetic effect on the part of ephedrine. It is scarcely to be expected, of course, that two different substances, however closely related, would possess physiological effects that are identical in all respects, but if it should be proved that the important actions of ephedrine are fundamentally different from those of epinephrine the present attitude of physicians toward ephedrine would have to be radically altered. On the whole, there appears to be no conclusive evidence that the actions of ephedrine that are of therapeutic importance are not sympathomimetic, and there is considerable evidence that they are. On the other hand, there is scarcely any respect in which the effects of ephedrine are identical with those of epinephrine, and there are several instances in which the two substances have opposite actions upon the same structure or function.

1. Action on lower forms of life

Very little work has been done along these lines. Macht (1929), who has made a systematic study of the toxic effects of various substances upon living plant organisms found that ephedrine was much less toxic than epinephrine to the seedlings of *Lupinus Albus*, a concentration of 1 in 5,000 of ephedrine having a phyto-toxic index of 75 per cent. This is in accord with other observations of the same author, indicating that a drug of animal origin is more toxic to plants than one of vegetable origin. In the sea crab, *Palaemon*, kept in 1 to 1000 solution of ephedrine, a temperature of 36° induces heat narcosis in 30 minutes (Fröhlich and Kreidl, 1921).

Nadler reported interesting results from experiments with the squid (*Loligo pealii*). He found that epinephrine and ephedrine, injected subcutaneously, produced local blanching, which was supposedly due to inhibition of smooth muscle of the chromatophore system. The effect of ephedrine differed from that of epinephrine in two respects, however. First, the blanching was much slower in its appearance when ephedrine was used, though it lasted 8 hours or more instead of 10 minutes, which was the duration of the epinephrine effect. Second, the animals injected with ephedrine showed a diffuse generalized reddish coloration excepting at the injected area; this coloration was also produced by intravascular or oral administration of the drug. Since excitement or irritation of the animal likewise caused the same color change, it was ascribed to stimulation by ephedrine of the central nervous system of the animal; epinephrine apparently had no such effect. These results indicate that the action of ephedrine upon this animal is twofold: a peripheral epinephrine-like one, and a stimulant one on the central nervous system.

Nadler also found that a number of substances produced peripheral effects opposite to those of epinephrine and ephedrine, namely, a local deep coloration at the site of injection. These were parathyroid and anterior pituitary extracts, posterior pituitary extract, and barium chloride. The last two are known to stimulate smooth muscle fibers directly, irrespective of their innervation (i.e., they are musculotropic), and the effects in the squid were thought to be due to contraction of the chromatophore musculature. He found that epinephrine or ephedrine, injected in sufficient quantity into the red zone produced by injection of any of these agents, was able to antagonize the effect and produce local blanching.

This is the only investigation, upon one of the lower forms of life, of the fundamental nature of the action of ephedrine. The conclusion was that the action of ephedrine is epinephrine-like (sympathomimetic) and not pituitrin-like (musculotropic).

2. Actions on the circulation

These are probably the most striking effects of ephedrine in the common laboratory animals, and it is somewhat strange that they were not investigated until comparatively recent times. If they had been, the present status of ephedrine might have been attained several decades ago.

a. The effect upon blood pressure. The first work—that of Miura (1887)—led to the conclusion that ephedrine is essentially a circulatory depressant. The doses used by him were excessive (fatal) ones, and cardiac depression evidently dominated the picture. Grahe (1895) reported a slight rise of blood pressure of curarized dogs upon subcutaneous or intravenous injection of ephedrine or pseudoephedrine, but his published tracings show barely detectable effects. He also found that subsequent injections led to a fall in pressure. The first demonstration of the characteristic pressor effect of ephedrine was that of Hirose (1915), who injected the drug intravenously in anesthetized rabbits. Amatsu and Kubota (1917) confirmed these results, and added the observation that the rise in pressure was not prevented by destruction of the medulla or by paralytic doses of chloral hydrate. Chen and Schmidt (1924) demonstrated similar effects in cats and dogs, and emphasized the relatively long duration of the effect of ephedrine, the diminution, disappearance, or reversal of the effect upon repeated injections, and the ability of ephedrine to raise blood pressure when taken by mouth. Since then many workers have contributed to the subject, and the principal features in the circulatory actions of ephedrine are well established.

Ephedrine causes a rise in blood pressure of anesthetized dogs when injected intravenously in dosage of 0.005 to 30 mgm. per kilogram, but the greatest effect is produced by doses of 1 to 10 mgm. per kilogram: following such injection, blood pressure rises by 100 or more millimeters of mercury and is maintained at this level for at least 15 to 25 minutes. In unanesthetized dogs, 5 to 10 mgm. of ephedrine per kilogram, by vein, was found by Pennetti (1928) to cause a rise in pressure lasting 3 to 4 hours.

The pressor effect of ephedrine appears to be less marked in rabbits than in cats and dogs (Kreitmair, 1927). The minimum pressor dose, injected intravenously, was found to be 0.05 mgm. per kilogram in rabbits, while 1/50th of this quantity was effective in cats.

Large quantities of ephedrine (40 to 65 mgm. per kilogram) injected intravenously in dogs, cause only a fall in blood pressure (Chen and Meek, 1926): these are close to the fatal dose. Kreitmair (1927) states that 10 mgm. or more per kilogram injected into a vein causes a fall in blood pressure in cats. This is the type of effect observed by Miura (1887), who apparently did not try smaller doses.

When the pressor effect of ephedrine is compared with that of epinephrine, several outstanding points of difference are apparent. First, the effect of epinephrine is much more intense but much less prolonged than that of ephedrine: under optimal conditions, employing intravenous injections in cats, the rise in pressure produced by epinephrine is 100 (Nagel, 1925) to 142 (Chen) times as intense as that of the same quantity of ephedrine, but the effect of ephedrine commonly persists 7 to 10 times as long as that of epinephrine (Chen). Second, the intensity of effect of epinephrine is so closely proportional to the quantity injected that the pressor response can be employed in assaying epinephrine preparations (United States Pharmacopoeia, Ninth Revision); this is distinctly not the case with ephedrine, the circulatory effects of which are by no means proportional to the quantity injected (Chen and Schmidt, 1924); they may be less from large doses than from smaller ones. Third, following an intravenous injection of epinephrine blood pressure frequently falls from the peak of the pressor effect to a subnormal level, rising slowly to normal; this is not true of ephedrine, following which pressure simply falls very gradually to normal (Kreitmair, 1927). Fourth, when epinephrine injections are repeated the same degree of effect will be obtained from each; with ephedrine, however, the first dose is by far the most effective one, and upon repetition the pressor effect of each becomes progressively less until it disappears completely or is replaced by a depressor effect (Chen and Schmidt, 1924). This latter feature has been noted repeatedly (Rowe, 1927; Rudolf and Graham, 1927; Kreitmair, 1927; Pittinger, 1928; Launoy and Nicolle, 1928) in cats, dogs, and rabbits, anesthetized or pithed. Its explanation involves factors which are also responsible for most, if not all, of the other differences between the circulatory effects of ephedrine and epinephrine, and the observations bearing upon this question may properly be considered at this time.

The extent to which the circulation becomes "tolerant" to repeated injections of ephedrine has been found to depend upon the size of the dose. Thus, comparatively large quantities (about 5 mgm. per kilogram), injected rapidly and at frequent intervals (5 to 10 minutes) very quickly become ineffective and soon lead to a depressor effect from each injection. On the other hand, small doses (0.02 to 0.05 mgm. per kilogram) may show cumulative effects (i.e., a step-like rise in pressure to a sustained high level) if injected at close intervals (Chen, 1926), and if time is allowed for pressure to recover between injections each may sometimes—though by no means always—produce the same pressor effect. The explanation advanced (Chen and Schmidt, 1924) for the decreasing effectiveness of repeated injections of ephedrine is that maximal pressor effects are soon developed, and that additional quantities of the drug are then incapable of producing further stimulant effects. It has been suggested (Chen and Meek, 1926) that the "receptors" with which ephedrine combines may be fewer in number, or more easily saturated, than those of epinephrine, which would account for the absence of progressive effects as the dose of ephedrine is increased above the optimum level. It seems probable that the greater persistence of ephedrine actions depends upon a more stable union with receptor substance than is the case with epinephrine and if the ephedrine receptors are saturated early the lack of progressive effect from repeated injections of ephedrine is accounted for. When the quantities of ephedrine are small this saturation would not be accomplished until a number of injections have been made. Such explanation appears to harmonize with experimental observations, and is the best available at present; it is, of course, purely hypothetical.

The depressor effect of ephedrine was attributed by Chen and Schmidt (1924) to cardiac depression—an effect which is well known and will be considered in the following section. It is wholly unlike the depressor action of epinephrine, which can be demonstrated with minimal doses and is apparently due to stimulation of vasodilator nerve endings (Dale: Journ. Physiol., 1906, xxxiv, 163): with ephedrine, a first injection is always purely pressor unless it is very large; a depressor effect from a small or moderate dose can be demonstrated only after maximal pressor effects have been produced by previous injections, and there is no evidence that any dose of ephedrine can produce a vasodilator effect comparable with that of epinephrine. The fact that the pressor effect of epinephrine is often followed by a depressor (vasodilator) one, while that of ephedrine is simply followed by recovery to normal, also indicates that the ability to stimulate vasodilators is either lacking completely in ephedrine, or is very much less conspicuous than is the case with epinephrine. It may be noted also that the pressor action of ephedrine is more affected by the condition of the subject than is the case with epinephrine. Animals whose blood pressures have been lowered by trauma, operative procedures, hemorrhage, etc., show much less pressor effect than normals, and are more likely to show only a fall in pressure following a moderate dose of ephedrine (Chen, 1925). Deep anesthesia and consequent hypotension also increase the probability of fall in pressure after only a few injections of ephedrine (Chen, 1925). Under such circumstances increasing the dose of ephedrine would be more likely to lead to fall than to rise in blood pressure—a contingency that is not encountered with epinephrine.

In brief, it appears that the capacity of ephedrine to raise blood pressure is limited by two factors: first, by its relative weakness as a circulatory stimulant, perhaps because there are only relatively few "receptors" with which it can combine, and additional quantities of the drug are incapable of producing further effects once these have been saturated; second, by the depressant action of ephedrine upon the heart—an effect that is masked by the pressor effect until the latter has become maximal, or unless overwhelming quantities are injected. Epinephrine is not subject to these limitations to anything like the same degree as ephedrine. This suggests that a mixture of the two drugs might possess the virtues of both—the intensity of epinephrine and the persistence of ephedrine—while minimizing their respective disadvantages—the evanescence of epinephrine and the danger of cardiac depression by ephedrine. This has actually been found to be the case.

Thus, Chen and Meek (1926) found that upon intravenous injection of ephedrine and epinephrine in dogs there was summation, both in intensity and duration, of the pressor effect. Launoy and Nicolle (1928) report an actual potentiation when such injections are made in unanesthetized rabbits, the rise in pressure being greater than the sum of the effects of both drugs given separately. Csépai and Doles-shall (1928) found that ephedrine sensitizes the human circulation to intravenous injections of epinephrine, the influence being especially marked in cases of hyperthyroidism; they believe that ephedrine sensitizes sympathetic nerve endings just as thyroxin sensitizes the cells to the action of hormones.

The action of ephedrine upon the human blood pressure has now been studied extensively, and with quite uniform results. The first study was that of Miller (1925), who reported rise in pressure in 70 out of 84 individuals given a dose of 50 to 125 mgm. of ephedrine orally or by subcutaneous injection. In 7 cases pressure was not altered, while in 6 it fell. The rise in pressure varied from a few millimeters to 65, and its duration was 6 to 8 hours. Similar results were reported by Rowntree and Brown (1926), Pollak and Robitschak (1926), Rudolf and Graham (1927), Hess (1926), Jansen (1926), Kesten (1927), Middleton and Chen (1927), Althausen and Schumacher (1927), Wu and Read (1927), Csépai and Fernbach (1928), Radoslav and Stoïcesco (1927), and Pennetti (1928). Anderson and Homan (1927) observed a rise in pressure in children given 15 mgm. of ephedrine hydrochloride. The results of Rowntree and Brown (1926), and of Hess (1926), indicate that blood pressure can be maintained at an elevated level for several days by means of daily administration of ephedrine. All observers agree that ephedrine is effectively absorbed following oral administration, and Hess (1926) has shown that rise in blood pressure also occurs following rectal administration of ephedrine, in dosage of 2 mgm. per kilogram, as suppository, in milk, or dissolved in the proctoclysis fluid. Intravenous injection was first tried by Miller (1925), subsequently by Jansen (1926). The effects are more marked than those of other routes of administration, but last only 15 to 30 minutes (Jansen).

The influence of disease upon the pressor effect of ephedrine in man has been studied by several workers. In Graves' disease, in which there is conspicuous sensitization to epinephrine, Pollak and Robitschek (1926) reported unusually marked pressor effects from ephedrine, but Csépai and Fernbach (1928) concluded that there is no sensitization to ephedrine in Graves' disease. In asthma, Thomas (1926) and MacDermot (1926) found no rise in pressure following oral administration of ephedrine, and a similar statement was made in an earlier review by Chen and Schmidt (1926). However, studies of larger series of cases by Althausen and Schumacher (1927) and Middleton and Chen (1927) have shown that ephedrine raises blood pressure in asthmatic patients, possibly less frequently than in normals, but to as high a level and for as long a time. Pennetti (1928) tried ephedrine in a single case of myxedema and found a fall in blood pressure from 210 to 145 mm. of mercury.

The effect of repeated doses of ephedrine, taken by mouth, upon the blood pressure of human beings has been investigated by Rowntree and Brown (1926) and by Chen (1928). It appears that when a therapeutic dose (50 mgm.) is taken by mouth every two to three hours the first causes the most marked rise in pressure, the subsequent ones causing further but smaller rises in the already elevated pressure and maintaining it at an abnormally high level as long as the drug is given regularly. These results are therefore similar to those obtained by intravenous injections of small doses (0.02 to 0.05 mgm. per kilogram) at short intervals in anesthetized dogs, and appear to indicate that the pressor effect of such dosage is not nearly maximal. The circulatory effect of a single dose of ephedrine, taken by mouth, evidently disappears completely within 14 to 24 hours, a second dose of the same size then producing practically the same effect as the first (Chen, 1928).

The effect of ephedrine upon venous pressure was studied by Chen and Meek (1926) in two dogs, one of which was atropinized. In each, a slight fall in venous pressure coincided with the rise in arterial pressure.

b. The action on the heart. The first investigations of the physiological effects of ephedrine disclosed its power of depressing the heart. Miura (1887) observed that lethal doses of ephedrine caused diastolic arrest of the frog's heart. Grahe (1895) found that ephedrine or pseudoephedrine, applied to the frog's heart by irrigation or injected intravenously, caused depression and irregularities, and that a heart arrested by either drug could not be made to beat by means of atropine, though a heart arrested by muscarine could be made to beat when treated with ephedrine or pseudoephedrine. Amatsu and Kubota (1917) obtained similar results with frog's heart studied by Engelman's and Straub's methods, confirming the inability of atropine (as well as camphor) to overcome the depressant effect of ephedrine. Chen and Schmidt (1924) found only depression of the frog's heart irrigated with ephedrine.

Subsequent investigations have confirmed the conclusion that ephedrine is essentially depressant to the frog's heart, while showing in addition that small quantities may exert an inconspicuous stimulant effect. Chen and Meek (1926) found that ephedrine sulphate, applied to the heart in concentration of 1 in 1,000, may cause acceleration by a few beats per minute, but a 1 in 100 solution was purely depressant to rate and amplitude. Barlow and Sollmann (1926), who perfused the heart by the method of Howell and Cooke, found pure depression with concentrations of ephedrine sulphate of 1 in 10^5 or stronger, rate, force and output being diminished, and with 1 in 10^3 dilutions complete heartblock was elicited; stimulation was occasionally observed with dilutions of the order of 1 in 10^7, being manifested as an increase in rate and amplitude, but the increase rarely exceeded 10 per cent. Kreitmair (1927) noted increase in amplitude of the frog's heart perfused by Straub's method with 1 in 10^4 ephedrine hydrochloride; rate was not affected, and higher concentrations were purely depressant, 1 in 100 causing arrest that could be combated by means of perfusion with 1 in 10^4 dilution of epinephrine, with calcium, or with histamine, but was not reversible upon simple perfusion with pure Ringer's solution, and was not affected by atropine. Gradinesco (1927) also found that epinephrine is able to restore the beat to the frog's heart arrested by perfusion with ephedrine. Gomes da Costa (1927) reported stimulant effects of dilute solutions of ephedrine upon the perfused frog's heart, but Lévy and Boyer (1927) found only depression when any effect was evident. Méhes and Kokas (1929) likewise observed depression of the frog's heart perfused with a 1 in 50,000 dilution of ephedrine, and believed that the effect was partly removed by small quantities of atropine.

The hearts of certain invertebrates have also been studied with respect to the effects of ephedrine. Lévy and Boyer (1927) studied the heart of the snail (*Helix pomatia*) and found systolic contracture with a 1 in 20 solution of ephedrine; weaker solutions (1 in 100, 1 in 1,000) caused a slowing in rate and an increase in strength of contraction, with periodic variations. Bain (1929) perfused the hearts of crabs (*Maia squinado*, *Cancer pogurus*, and *Carcinus moenas*) with ephedrine, among other drugs, including epinephrine which, in 1 to 50,000 dilution caused a marked increase in rate and tone of the hearts: ephedrine was used in the same dilution as epinephrine, and produced no effect whatever. Apparently a stronger solution of ephedrine was not used, so that one can conclude only that ephedrine is weaker than epinephrine in its effects upon these hearts, as upon all others.

The isolated heart of the toad was perfused with ephedrine and pseudoephedrine by Loo and Read (1928): they usually found depression of amplitude of beats with 1 in 20,000 ephedrine following pseudoephedrine but ocasionally ephedrine caused acceleration.

The turtle's heart was perfused with ephedrine by Chen and Meek (1926): dilutions of 1 in 10,000 sometimes accelerated the rate slightly, but 1 in 1,000 or 1 in 100 caused bradycardia, usually with decrease in amplitude, culminating in diastolic arrest.

The action of ephedrine on the mammalian heart was investigated by Chen and Schmidt (1924) and by Chen and Meek (1926). Pulse rate in the intact unanesthetized dog is usually slowed, occasionally accelerated, when ephedrine is injected subcutaneously or intravenously; in the anesthetized animal acceleration is commonly observed following intravenous injection of less than 1 mgm. per kilogram, though after larger doses (1 to 20 mgm. per kilogram) slowing is commonly seen. Atropine completely abolishes or prevents the bradycardia, which is thus to be regarded as a reflex effect of the rise in blood pressure, the slowing being greater in animals whose cardio-inhibitory centers are not depressed by anesthesia. This explanation is, however, called into question by the recent experiments of Pennetti (1928), who found that section of the vagi or injection of atropine in unanesthetized dogs does not usually accelerate the heart slowed by ephedrine. Confirmation of these results is highly desirable. Coelho (1929) reports that in dogs narcotized with chloralose, ephedrine, in dosage of 1 to 20 mgm. per kilogram, causes acceleration of the heart.

The strength of the beats of mammalian hearts has also been found to be increased by ephedrine. Chen and Schmidt (1924) recorded the contractions of part of the right ventricle (myocardiograph) and found them markedly increased by ephedrine. The effect was not prevented by section of the vagus nerves or by atropine, was not due to an atropine-like effect upon cardio-inhibitory nerves, and was fully comparable with that of electrical stimulation of the accelerator nerve or of injection of epinephrine. They also showed that ephedrine caused increase in rate and amplitude of ventricular contractions when applied locally to the stellate ganglia—a feature in action that is not shared by epinephrine (Chen and Meek, 1926). Intravenous injection of ephedrine caused still further acceleration and augmentation. Large quantities of ephedrine (40 to 55 mgm. per kilogram by vein) are apt to cause acute cardiac depression (Chen and Meek, 1926). The cardiac stimulant action of small quantities of ephedrine and the depressant action of large quantities have also been observed by Kreitmair (1927) on cats and by Launoy and Nicolle (1928) on rabbits. Chopra, Dikshit, and Pillai (1929) found increase in auricular contractions in cats given 2 mgm. injections, the ventricles being unaffected, while with 5 mgm. both auricles and ventricles were depressed.

It has been shown by La Barre (1928) that ephedrine does not lead to ventricular fibrillation in cats under chloroform anesthesia; in this respect ephedrine differs from epinephrine.

Studies of the effect of ephedrine upon the cardiac output of dogs were made by Chen and Meek (1926) by means of cardiometric and teleoroentgenographic methods. They concluded that in the (anesthetized, atropinized) dog there is a distinct and constant increase in voume output per minute at the time of increase in pulse rate and rise in blood pressure. Wilson, Pilcher, and Harrison (1928) employed the Fick principle to measure cardiac output of unanesthetized dogs, and found that ephedrine caused an increase in minute volume, especially when the drug was given subcutaneously or by mouth. Halsey, Reynolds, and Blackberg (1927) employed the same methods but obtained opposite results, i.e., ephedrine was found to decrease the cardiac output of unanesthetized dogs as well as of dogs narcotized with chloroform or chloral hydrate. It should be noted that results obtained by this procedure are frequently opposed to those obtained by other methods. For example, digitalis, which has been universally regarded as a stimulant to cardiac muscle and is found to be such by other methods of investigation, decreases cardiac output as measured by the Fick method and appears to be essentially a cardiac sedative (Harrison and Leonard: Jour. Clin. Invest., 1926, iii, 1); and quinidine and chloral hydrate, which, by other methods of investigation, are shown to be marked cardiac depressants, appear as cardiac stimulants according to the results obtained by this method (Halsey, Reynolds, and Blackberg, 1927). Until such discrepancies are satisfactorily explained it is impossible to evaluate the results obtained with respect to ephedrine.

Electrocardiographic studies made by Chen and Meek (1926) in unanesthetized and anesthetized animals, showed that small doses (5 to 10 mgm. per kilogram by vein in dogs) did not alter the contour of the curve, apart from the T-wave, which might be flattened, inverted, or occasionally augmented. Massive doses (40 to 75 mgm. per kilogram), given intravenously to dogs and rabbits, appeared to depress the automatic and conducting systems in descending order, that is, from sino-auricular node to the ventricular terminations of the Purkinje system: there were, in the order of their appearance, bradycardia, prolongation of the P-R interval, partial auriculo-ventricular block, nodal rhythm, ventricular automatism or extrasystoles, bundle branch block, finally ventricular fibrillation. Similar results were obtained by Coelho (1928) in dogs narcotized with chloralose.

The isolated mammalian heart has also been studied: Chen and Schmidt (1924) and Chen and Meek (1926) found that the rabbit's heart perfused according to Langendorff's method was stimulated in rate and strength of beats by low concentrations (1 in 100,000) of ephedrine sulphate, while stronger solutions (1 in 10,000, 1 in 5,000) caused depression of both rate and strength; still stronger solutions (1 in 2,000) brought about partial block, and 1 in 1,000 caused prompt failure (Chen and Meek, 1926). Similar results were obtained by Chopra, Dikshit, and Pillai (1929), and by Pennetti (1928); the latter found that epinephrine was able to revive a heart arrested by ephedrine.

The effects of ephedrine upon the human heart have received considerable study. The effect upon pulse rate was observed by Chen and Schmidt (1924) in a small series of cases, all of whom showed a slowing after oral or subcutaneous administration of ephedrine. Miller (1925), in a much larger series, found slowing of the pulse during the rise in blood pressure in the majority, but in 16 of his 84 subjects pulse rate was accelerated by ephedrine. Pulse rate and blood pressure returned to normal at about the same time. Rowntree and Brown (1926) noted acceleration of the pulse as frequently as slowing, and Middleton and Chen (1927) observed that acceleration was produced more frequently than slowing. In the experience of Hess (1926) and of Rudolf and Graham (1927), a decrease in pulse rate was the more frequent result of ephedrine, but in the cases of Jensen (1926) acceleration was the more frequent. In some cases in all these series pulse rate was unaffected. On the whole, the effect of ephedrine upon the rate of the human heart appears to be of the same nature as that upon the dog's heart, namely, acceleration or slowing, depending upon conditions which are not well understood. The influence of atropine upon the cardiac effects of ephedrine in man has apparently not been investigated, but it may be inferred that bradycardia following a therapeutic dose of ephedrine is a reflex effect of the rise in blood pressure.

Evidence that ephedrine increases the strength of contractions of the human heart was obtained by Miller (and Pendergrass) (1925) by means of fluoroscopic observations of three individuals, in every one of whom the excursion of the ventricular and aortic shadows was greater after ephedrine than before. At the same time the apex impulse became visibly and palpably more forceful and the heart sounds became louder. These observations furnish an explanation of the palpitation which is commonly complained of by patients receiving ephedrine. Miller (1925) has also called attention to the occasional appearance of systolic murmurs in patients who had normal sounds before ephedrine was given, and to the intensification of existing systolic murmurs by ephedrine. These murmurs may be heard at the apex alone, at the base alone (in either aortic or pulmonary area), or in all these areas. He suggested that they might be the result of distention of the cardiac chambers leading to the relative stenosis of aortic or pulmonary orifices, or to relative insufficiency of the mitral valve.

Electrocardiographic studies of the effects of ephedrine in man were made by Middleton and Chen (1927) in 11 patients, the drug being taken by mouth; seven showed no change, four developed ventricular or auricular extrasystoles, these being most marked in a patient with chronic myocarditis in whom systolic blood pressure fell 30 mm. following ephedrine. Pennetti (1928) studied the electrocardiograms of 8 subjects with normal cardiovascular systems upon subcutaneous injection of 50 mgm. of ephedrine. Five of these showed perfectly normal tracings after the drug was given, while in three there was some change—decrease or increase—in height of the R wave and prolongation of the S wave, and in one the T wave became diphasic.

The observations bearing upon the action of ephedrine upon the heart may be summarized as follows: there is no doubt that ephedrine, in large dosage, is depressant to the amphibian or mammalian heart, and may cause acute cardiac failure. This action is apparently exerted directly upon the muscular and neuromuscular tissues of the heart, and is independent of effects upon the cardiac nervous mechanism. The cardiac stimulant effect of smaller quantities of ephedrine is likewise well marked in the case of the mammalian and human heart, less so in the amphibian heart. This effect is fully comparable with that of excitation of the accelerator nervous mechanism of the heart, by means of electrical stimuli or epinephrine. The effect of ephedrine differs from that of epinephrine in that it is apparently exerted not only upon the extreme peripheral parts of the accelerator system, but upon its ganglia as well.[1] In the cardiac effects of ephedrine one sees the same general differences from epinephrine that are evident in the effects upon blood pressure: ephedrine effects are less intense but much more prolonged, and upon increasing or repeating the dose of ephedrine the stimulant effect is increased little or not at all, or may be replaced by a depressant effect. The ability of ephedrine to increase the rate and force of heart beats is limited not only by an apparently small number of receptors, but also by its capacity for depressing heart muscle. Its cardiac stimulant effect cannot be made as intense as that of epinephrine by increasing the dosage and this fact, together with the deleterious effects of large doses upon heart muscle, make the intravenous or intracardiac administration of ephedrine inadvisable when stimulation is needed in an emergency.

c. The action on blood vessels. Ephedrine produces vasoconstriction. This was first demonstrated in 1917 by Amatsu and Kubota by means of perfusion experiments. They observed constriction of vessels of frogs' legs upon perfusion with a concentration of 1 in 10,000 of ephedrine hydrochloride; the vessels of the ear of the rabbit were constricted by solutions ranging from 1 in 2,000 to 1 in 20,000; constriction was also noted in the perfused vessels of the intestine, spleen, and kidney of the dog. Their results have been confirmed by perfusion experiments made by Chen and Schmidt (1924) on the dog's kidney, by Chen and Meek (1926) on the kidney, spleen, and leg of the dog, by Barlow and Sollmann (1926) and by Méhes and Kokas (1929) on the frog, by Loo and Read (1928) on the toad, the latter finding a 1 in 20,000 solution effective. Other workers, while agreeing that ephedrine is a vasoconstrictor, found it a much less powerful one than these results would indicate. Thus, Kreitmair (1927) found constriction of frog's vessels with a 1 in 10 dilution of ephedrine, but none with a 1 in 100 solution; Gradinesco (1927) found only slight constriction with a 1 in 100 solution, and Schaumann (1928) obtained only slight constriction with concentrations less than 1 in 1,000. The last-named investigator found that a very small amount of epinephrine augmented the constrictor action of ephedrine, and that repeated applications or an increase in concentration of ephedrine were less effective, ineffective, or might cause dilatation of vessels.

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[1] This has been recently denied by Tainter (1929) who found that ephedrine, applied to the stellate ganglion, caused cardiac acceleration only exceptionally, and that similar effects could be produced by application to the pleura itself. He calls attention to the acidity of ephedrine solutions as a probable factor in the result obtained by Chen and Schmidt (1924).

Plethysmographic investigations have also disclosed the ability of ephedrine to constrict blood vessels, and have furnished additional information concerning its relative effectiveness upon different parts of the vascular system. Chen and Schmidt (1924) reported that intravenous injection of ephedrine in dogs caused immediate decrease in volume of the kidney only, and this decrease was followed by increase to a level far above normal. Increase in volume as blood pressure rose was usually observed in the intestines and invariably in the leg. Chen and Meek (1926) obtained similar results; they also recorded volume of the spleen and found it usually decreased during the rise in blood pressure produced by ephedrine. Rudolf and Graham (1927) noted that the volumes of intestines and leg of the dog were slightly increased at first, but subsequently decreased, indicating delayed vasoconstriction. Gradinesco and Marcu (1927) reported increase in splenic volume; kidney volume was increased following small doses, but with large ones it was first decreased, then increased. Lim, Necheles and Ni (1927), who recorded the volume of the viviperfused stomach of the dog, obtained evidence of vasoconstriction by ephedrine, but a slight increase in volume was sometimes noted.

These results leave no doubt concerning the ability of ephedrine to constrict certain blood vessels, nor concerning its status as a vasoconstrictor that is much less powerful and uniform in its effects than epinephrine. Yet it appears that the vasoconstrictor action of ephedrine, like that of epinephrine, is essentially peripheral, and is not dependent upon stimulation of the vasomotor center or other parts of the central nervous system. This was shown by Amatsu and Kubota (1917), and by Chen and Schmidt (1924), who found ephedrine effective in raising the blood pressure of animals whose central nervous systems were destroyed or paralyzed. The same conclusion was reached by Marcu and Gheorghiu (1927) as a result of observation of simultaneous changes in carotid and crural blood pressures, and by Heymans (1928), who employed crossed-circulation experiments to exclude the central nervous system; the former found that ephedrine still raised blood pressure after exclusion of cardiac and splanchnic effects. But since plethysmographic experiments have shown that vasoconstriction is evident only in certain organs (kidney, spleen) as blood pressure rises following ephedrine it is clear that the effect is not exerted in the same degree upon all blood vessels—a conclusion that is equally applicable to epinephrine.

Concerning the part of the vascular bed that is affected by ephedrine, little information is available. Kreitmair (1927) reported that a 1 per cent solution of ephedrine, locally applied to the web or tongue of a frog, causes constriction of arterioles and obliteration of capillaries. Chen (unpublished) studied the circulation of the frog's tongue, web, mesentery, and kidney, but was unable to detect any significant changes upon local application or intravenous injection of ephedrine until a sufficient quantity had been given to depress the heart, when the observed effects could be attributed wholly to cardiac depression. H. C. Hou (personal communication) obtained practically the same result. It appears, therefore, that ephedrine has not the intense constrictor action upon the extremely peripheral parts of the vascular bed that is so conspicuous a feature in the case of epinephrine. This may explain to a considerable degree the greater readiness with which ephedrine is absorbed into the circulation; it also makes ephedrine unsuitable for combination with local anesthetic mixtures.

The action of ephedrine upon blood vessels that are not markedly constricted by epinephrine (coronary, pulmonary, cerebral) has not been studied systematically. Chen and Schmidt (1924) found that ephedrine, like epinephrine, increased the outflow from the coronary vessels of the rabbit's heart perfused by Langendorff's method. Schmidt (1928) reported increase in venous outflow from the brains of dogs and cats given pressor doses of ephedrine, as well as epinephrine, but pituitrin had the same sort of effect. The effects upon the pulmonary circulation apparently have not been studied.

Some information has been obtained concerning the action of ephedrine upon human blood vessels. Marcu (1926) applied a plethysmograph to one arm and a cuff for sphygmomanometry to the other. He concluded that minimal doses of ephedrine (less than 1 mgm. by vein) caused dilatation followed by constriction of abdominal vessels, while small doses (less than 10 mgm.) caused generalized constriction in splanchnic and other vessels; larger doses had the same general effect, but constriction of abdominal vessels became relatively more marked. Apparently the splanchnic circulation of man is most susceptible and is most powerfully affected by ephedrine, and this is in harmony with the results of plethysmographic experiments in animals. Rowntree and Brown (1926) studied the effects of intradermal injection of 10 per cent ephedrine in saline solution. The reaction was a small red central area surrounded by a patchy white border of irregular outline and inconstant appearance; reflex erythema was frequent. Epinephrine, similaly injected, caused a small white central area, surrounded by a zone of erythema. This confirms the results obtained by observation of the effects of ephedrine on capillaries of the frog in indicating that ephedrine has little or no constrictor effect upon capillaries. The ability of ephedrine to constrict the vessels of the nasal mucous membrane of man when the drug is taken by mouth has been proved repeatedly and will be considered in the section dealing with clinical uses.

3. The action on respiration

Apart from its effect upon the respiratory passages, which are due wholly to peripheral actions, ephedrine is a stimulant to the respiratory center, resembling caffeine in its effects. In intact animals small doses of ephedrine (5 mgm. per kilogram subcutaneously, 1 mgm. per kilogram by vein) have no significant effect upon respiratory rate or depth, and the same is true of human beings given therapeutic doses (Jansen 1926). In anesthetized animals the results appear to be somewhat variable in detail but stimulation is a common result. Fujii (1925) found that the respiration of urethanized rabbits was increased in rate and decreased in depth by ephedrine in dosage of 10 mgm. per kilogram. Kreitmair (1927), using cats anesthetized with urethane and ether, found that 5 mgm. of ephedrine per kilogram caused increase in depth of respiration, rate being unaffected.

Suzuki (1928) gave larger doses (30 mgm. per kilogram) to rabbits and noted as a rule an increase in depth with decreased rate of breathing, though occasionally rate was increased markedly. Schmidt (1929) found that ephedrine was more regularly effective than any of the conventional respiratory stimulants in combating extreme respiratory depression due to morphine. Toxic or lethal doses of ephedrine always produce acceleration of respiratory rate immediately before final failure of breathing, in intact or anesthetized animals (Miura, 1887; Chen, 1926; Kreitmair, 1927); this may be due to a large extent to acute circulatory depression.

The action of ephedrine upon the respiratory center seems to consist of two distinct components: first, an increase in blood supply of the center, due to the pressor effect; second, a direct stimulant action upon the cells of the center. The result of ephedrine action is therefore equivalent to that of a combination of epinephrine and caffeine. Ephedrine appears to be the most useful single respiratory stimulant that is available at present (Schmidt, 1929).

4. *The action on smooth muscle*

In the effects that have been considered up to this point ephedrine differs only quantitatively from epinephrine. When the actions of the two agents are compared upon smooth muscle in general however, it is soon evident that the effects of ephedrine are sometimes opposite to those of epinephrine. Since the latter are due, in so far as is known at present, wholly to stimulation of the sympathetic innervation of the muscle, it is clear that ephedrine either lacks this power or else applies it to the various parts of the sympathetic system with relative intensities that are different from those of epinephrine.

a. Pupil. Ephedrine produces mydriasis when applied locally to the conjunctiva or when absorbed into the circulation. This was first demonstrated by Miura (1887) and by Takahaski and Miura (1889) in dogs, cats, and rabbits, as well as humans; the pupils of chickens and pigeons were not dilated by ephedrine. These earliest workers left little to be added to the analysis of this feature in the action of ephedrine. They found that the light and accommodation reflexes were not abolished by the drug; that electrical stimulation of the oculomotor nerve caused contraction of the pupil dilated by ephedrine;

that section of the cervical sympathetic nerve or extirpation of the superior cervical ganglion did not prevent ephedrine mydriasis; that the latter could be diminished or overcome by means of muscarine, pilocarpine, or physostigmine, as well as nicotine; that atropine did not cause further mydriasis after ephedrine had produced its complete effect. They concluded (1889) that ephedrine mydriasis is due to stimulation of the sympathetic pupillo-dilator mechanism and does not involve paralysis of the parasympathetic (oculomotor) pupilloconstrictors. The results have been confirmed in all respects by Grahe (1895), by Hirose (1915) and Miura (1912) on enucleated eyes of frogs, by Chen and Schmidt (1924) on the eyes of dogs, cats, rabbits and men, by Koppányi (1928) on the eyes of guinea-pigs, and by Poos (1927) on the isolated sphincter and dilator muscles of the eyes of rabbits and calves. The latter was able to show that ephedrine—like epinephrine and cocaine—causes increase in tone of the dilator muscle, decrease in that of the sphincter; the stimulant effect upon the dilator was augmented by increasing the alkalinity of the solution. This may explain the result obtained by Munch (1928), confirmed by Swanson, Thompson and Rose (1929), that ephedrine base is a more powerful mydriatic in the cat than is the alkaloidal sulphate or hydrochloride.

Chen and Schmidt (1924) confirmed the results of Miura, adding the observation that ephedrine does not cause loosening of corneal epithelium. Kreitmair (1927) stated that while ephedrine injected intravenousy is about equally effective in causing mydriasis in dogs, cats, and rabbits, local application to the conjunctiva causes much less mydriasis in cats than in the other animals.

Comparing the pupillary effects of ephedrine with those of epinephrine, an essential difference is at once evident in the fact that while epinephrine has little or no effect upon the normal pupil, whether the drug is applied locally or injected intravenously, ephedrine is a highly effective dilator of the normal pupil, by any mode of administration. Schmidt (unpublished results) recently compared the effects of the two drugs upon the pupils of three rabbits each of whom had had the left superior cervical sympathetic ganglion removed several months previously: epinephrine, locally applied to both eyes or injected intravenously, dilated only the pupil of the operated side, while ephedrine, similarly exhibited, dilated both pupils, but the normal one more markedly than the other; pituitrin, locally applied, did not dilate either pupil. In these animals, as well as in the ones previously used by Chen and Schmidt (1924), cocaine dilated only the normal pupil. It is obvious that denervation does not sensitize the pupil to the effect of ephedrine as it has long been known to do to that of epinephrine. On the other hand, the structures upon which ephedrine acts to produce mydriasis do not degenerate after excision of the superior cervical ganglion, as appears to be the case with those upon which cocaine acts. Yet the action of all three drugs is essentially peripheral, as shown not only by the fact that the effect is limited to the eye to which they are applied, but also by the results obtained with the excised surviving muscle (Poos, 1927). The sensitization of the denervated pupil to epinephrine was attributed by Meltzer and Auer (1904) to the removal of inhibitory influences exerted by the ganglion upon the peripheral receptors with which epinephrine reacts, assuming that the latter do not degenerate under such conditions. On this basis, it would be necessary to conclude that cocaine acts upon receptors all of which degenerate following removal of the ganglion, and that ephedrine, the effects of which are weakened but not abolished by such removal, acts partly upon cocaine-like receptors and partly upon epinephrine-like ones.

b. Gastro-intestinal tract. In contrast with the effects of epinephrine, which are uniformly like those of stimulation of the sympathetic innervation of this system, the effects of ephedrine appear to be irregular and uncertain.

The effects upon the œsophagus were studied by To (1921), using the isolated organ of the frog. He found that ephedrine relaxed its tone in concentration of 1 in 2,000, and exerted a potentiating effect when given together with atropine or papaverine.

The crop muscles of the pigeon were found by Hanzlik and Butt (1928) to be thrown into contraction by ephedrine in dosage of 10 to 20 mgm. per kilogram; the effect involved both circular and longitudinal musculature, lasted 5 to 10 minutes, and was not prevented by atropine, though it was reduced by cocaine.

The effects of ephedrine upon the stomach in situ were studied in unanesthetized dogs with permanent fistulae by Kinnaman and Plant

(1927); they gave 5 mgm. of ephedrine per kilogram by vein, and found prompt and marked relaxation of gastric tone with inhibition of gastric motility, lasting 4 to 5 hours. Schmidt (unpublished) recently had the opportunity of repeating this experiment upon a single dog; following subcutaneous injection of 1 mgm. of ephedrine per kilogram, there was relaxation of tone and inhibition of gastric peristalsis for about 2 hours. In none of these experiments was there any trace of a stimulant action by ephedrine upon the gastric muscle of the unanesthetized dog, and inhibition (the epinephrine-like effect) was uniformly observed. M'Crea and Macdonald (1928) found that ephedrine, like epinephrine, inhibited gastric peristalsis and caused fall in intragastric pressure of anesthetized cats. The effects of ephedrine upon the human stomach have also been investigated. Pollak and Robitschek (1926) made roentgenologic studies: they observed an increase in gastric peristalsis, leading to expulsion of the barium meal into the duodenum, ½ to 1 minute after the subject had swallowed 20 drops of 10 per cent solution of ephedrine. They state that epinephrine caused a similar effect, which, they believe, may have been due to direct excitation of the musculature or to reflex stimulation consequent upon irritation of the mucous membrane. Marcu and Savulesco (1928) recorded gastric motility by means of a balloon which was swallowed and connected to a water manometer; upon intravenous injection of 1 cc. of a 1 in 500,000 solution (0.002 mgm.) of ephedrine they observed transitory contraction of the stomach, 0.02 to 0.05 mgm. had no effect, while 0.1 mgm. caused inhibition of contractions for about 10 minutes; upon intravenous injection of 20 mgm. of ephedrine, there was marked and prolonged inhibition of gastric movements, with a stimulant after-effect.

The effects upon the small intestine in situ have received less attention. Using unanesthetized dogs with fistulae of the ileum, Kinnaman and Plant (1927) found that ephedrine, injected intravenously, uniformly caused immediate relaxation and inhibition of motility, followed by a stimulant effect that became more marked as the dose was increased. With 0.5 to 1 mgm. per kilogram inhibition was marked, lasted 30 minutes to 2 hours, and was followed by only slight stimulation, but with 5 mgm. per kilogram the period of inhibition was shorter and the stimulant after-effect was more marked. Schmidt (unpublished experiments) tried the effect of intramuscular injections of 2 mgm. of ephedrine per kilogram in four unanesthetized dogs with fistulae of the ileum, making 13 observations in all. In eight, there was pure decrease in motility, ranging from slight to marked; in two there was no distinct effect; in two there was brief inhibition followed by increase in motility; in only one case was there pure stimulation after ephedrine, and this was insignificant compared with the effect of local application of an aromatic water or intramuscular injection of 5 mgm. of morphine.

The large intestine in situ showed only depression of tone and motility in every one of the few observations made. Kinnaman and Plant (1927) found this to be the case in unanesthetized dogs with colonic fistulae, and Schmidt (unpublished), using two such dogs, saw distinct decrease in tone and prolonged inhibition of motility following intramuscular injection of 2 mgm. of ephedrine per kilogram, if active movements were present before the drug was given; if not there was no effect. As far as we know there has never been any sign of a stimulant effect by ephedrine upon the large intestine in situ.

The results of experiments upon the gastro-intestinal tract in situ therefore indicate that the effects of ephedrine are, on the whole, very similar to those of epinephrine. With isolated strips of intestinal muscle, surviving in a warm saline solution, the results are much less uniform, some workers finding that ephedrine is only depressant, others reporting depression and stimulation, still others observing only stimulation. Thus, Amatsu and Kubota (1917) found ephedrine to be essentially depressant to isolated intestine of cats and rabbits, and the same result was obtained by To (1921), by Fujii (1925), and by Chen and Schmidt (1924) in rabbits. The last-named investigators found that the inhibitory effect of ephedrine could be readily overcome by means of pilocarpine or barium, and was not prevented by nicotine, thus showing that the effect was not due to depression of parasympathetic nerve endings, muscle fibers, or intrinsic ganglia (plexus of Auerbach). Subsequent workers have failed to confirm these results. Nagel (1925) found ephedrine to be purely stimulant to the isolated intestine of the rabbit and cat; the inhibitory effect of epinephrine could be overcome by ephedrine. Kreitmair (1927) found the isolated intestine of the cat to be relaxed by low concentrations (1:1,000,000 to 1:100,000) of ephedrine, but slightly stimulated by a stronger one (1:6,000); the latter effect could be prevented completely by atropine. Reinitz (1928) reported that isolated rabbit intestine was sometimes inhibited, often stimulated, sometimes inhibited and then stimulated, by the same concentration of ephedrine; he stated that atropine had no significant influence upon the stimulant response. Méhes and Kokas (1929) reported stimulation of isolated rabbit intestine by weak concentrations (1:150,000 to 1:50,000) of ephedrine, relaxation with a stronger one (1:10,000). Rudolf and Graham (1927) found only slight and transitory depressant effects by ephedrine upon isolated rabbit intestine. Lim and Chen (1928) noted only stimulation of cat intestine, isolated but with intact circulation, upon the addition of ephedrine. De Eds, Rosenthal, and Voegtlin (1928) reported pure stimulation of rabbit intestine exposed to a 1:5,000 solution of ephedrine, and Halsey (1928) found no instance, among many preparations of isolated rabbit intestine, of anything but stimulation by ephedrine.

Isolated large intestines of the rabbit were found by Kreitmair (1927) to be affected like the small by ephedrine, i.e., they were depressed by weak solutions, stimulated by strong ones and the latter effect could be prevented by atropine. Thienes (1929) reported that epinephrine depression of isolated large intestines of cats, rabbits, dogs, rats and guinea-pigs was antagonized by ephedrine.

It may safely be assumed that any of these preparations would have been inhibited by epinephrine, so that it is very evident that the effects of ephedrine upon isolated muscle of the gastro-intestinal tract are inconstant. A probable explanation for this will be presented later (page 52). It should be pointed out here that the effects of ephedrine upon movements of the gastro-intestinal tract in situ appear to be much more nearly like those of epinephrine than is the case when the two agents are tested upon isolated muscle preparations. The reason for this is unknown: it is possible that central nervous influences or indirect actions through the suprarenal glands (see page 55) play a part in these effects of ephedrine in the living animal. Whatever the explanation, the effects upon the gastro-intestinal tract in situ are those which are of therapeutic importance, and there is no evidence at present that ephedrine can properly be employed as a stimulant to gastro-intestinal motility.

c. Uterus. All of the data available at present were obtained with isolated tissue excepting a few experiments of Chen and Schmidt (1924), who found that the dog's uterus in situ was stimulated by ephedrine. To (1921) reported that the isolated uterus of the rabbit or rat was depressed by dilute solutions of ephedrine (1:20,000 and 1:100,000 to 1:10,000 respectively), while stronger solutions (1:10,000 and 1:3,300 to 1:2,000 respectively) caused stimulation. Chen and Schmidt (1924) found that the isolated rabbit uterus was uniformly stimulated by ephedrine, with only one exception—the uterus of a recently delivered rabbit. Stimulation was the only effect of ephedrine upon isolated uterus in the experiments of Fujii (1925) on rabbits, of Nagel (1925) on guinea pigs, of Kreitmair (1927) on rabbits, of De Eds and Butt (1927) and De Eds, Rosenthal, and Voegtlin (1927) on rabbits and guinea-pigs, of Thienes (1929) on cats, rabbits, dogs, rats and guinea-pigs, of Reinitz (1928) on rabbits, and of Curtis (1929) on guinea-pigs and cats. The uterus of the albino rat, however, is uniformly relaxed by ephedrine (Liljestrand, 1927).

These results are quite unlike those obtained with epinephrine, which usually relaxes the isolated non-pregnant uterus of the cat and frequently relaxes the non-pregnant guinea-pig uterus. In fact Thienes (1929) found that ephedrine prevented the inhibitory effect of epinephrine upon various uteri. Reinitz (1928) reported that very small quantities of ephedrine augment the (stimulant) effect of epinephrine upon the isolated rabbit uterus, but larger quantities reduce it.

In general, the action of ephedrine upon the isolated uterus is characteristically a stimulant one, and bears no constant relation to the action of epinephrine. Whether the same is true of the effects upon the intact uterus in situ has not been determined, for no experiments have as yet been made with animals whose uteri are relaxed by epinephrine.

d. Urinary tract. Hofbauer (1928) tested the effect of ephedrine upon the isolated ureter of the pig: he found that the rate of contractions of both circular and longitudinal muscle was increased by ephedrine, and that it was occasionally possible, by means of ephedrine, to restore contractions after they had been arrested by sodium glycocholate; the effects of epinephrine were qualitatively the same but it was a much more powerful stimulant than ephedrine. His results have been confirmed by Roth on the dog's ureter.

Macht (1929) studied the effects of ephedrine upon the trigonal and fundus portions of the urinary bladders of rabbits, cats and rats. It has been shown repeatedly that epinephrine causes contraction of the trigone and relaxation of the fundus. Ephedrine caused contraction of both portions. Liljestrand (1927) obtained the same results with the rabbit's bladder.

e. Bronchi. One of the most useful therapeutic actions of ephedrine is its ability to relieve or to prevent the paroxysms of asthma. Animal experimentation has shown from the start that ephedrine, like epinephrine, is able to relax bronchial spasm induced by various poisons. Amatsu and Kubota (1917) were the first to demonstrate this effect in rabbits whose bronchi had been thrown into spasmodic contraction by means of pilocarpine, muscarine, or peptone. They also found that isolated bronchial muscle of the cow was relaxed by ephedrine, even in such low concentration as 1 in 80,000. These results led them to recommend ephedrine in the treatment of asthma. Chen and Schmidt (1924) observed relaxation of the bronchial spasm produced by physostigmine in a dog, and stated that the effect of ephedrine was weaker than that of epinephrine. Kreitmair (1927), Villaret, Justin-Besançon, and Vexenat (1929), and Swanson (1929) have confirmed these results by various methods, but Halsey (1928) reported only exceptional bronchodilatation by ephedrine. It is generally agreed that ephedrine may fail to relax bronchial spasm when epinephrine is effective. It is generally assumed that the bronchodilator action of ephedrine is analogous to that of epinephrine and is due to stimulation of sympathetic nerves, which are inhibitory to this muscle; this has not, however, been definitely proved to be true. The effect is largely if not wholly peripheral, for it is elicited in excised tissue and in pithed animals.

5. Action on secretions

a. Saliva. Grahe in 1895 studied the action of ephedrine and pseudoephedrine on the submaxillary flow in a dog and found that the first intravenous injection has no effect while repeated injections gradually diminish the flow. Chen and Schmidt, and Chen investigated the same question in a series of dogs. In anesthetized animals, ephedrine in a dosage of 1 to 2 mgm. per kilogram produces inconsistent results. Occasionally it increases the submaxillary flow, and this occurs in spite of atropinization, but in the majority of cases it has no effect. Larger doses (25 mgm. per kilogram or more) in non-anesthetized dogs may cause profuse salivation. When a dose slightly below the M.L.D. is administered, the increase in salivary flow is a constant feature.

b. Gastric secretion. Chen in Lim's laboratory studied the action of ephedrine on the gastric secretion in dogs with Pavlov or Heidenhain pouches. Ephedrine injected subcutaneously unmistakably increases the gastric secretion both in volume and in acidity, although to only a small extent. There is no difference between the Heidenhain and Pavlov preparations.

c. Pancreatic secretion. In anesthetized dogs with a cannula in the pancreatic duct ephedrine, given intravenously, does not change the pancreatic secretion, as shown by Chen. In non-anesthetized dogs with a pancreatic fistula, subcutaneous injections of ephedrine also gave negative results. Fonseca and Trincao (1928) reported that ephedrine caused decrease in pancreatic secretion.

d. Intestinal secretion. Dogs with Thiry-Vella fistula do not show any response in their intestinal secretions to the subcutaneous injection of ephedrine, as reported by Chen.

e. Bile. In acute experiments with anesthetized dogs, there is no demonstrable alteration of bile flow after ephedrine injected intravenously (Chen). The same can be said for non-anesthetized animals with a pancreatic biliary fistula when ephedrine is injected subcutaneously. Kreitmair, using larger doses (50 to 100 mgm. per dog), found an increase of bile flow from the biliary fistula, with a reduction of the dry matter. The increase in volume continues for more than three days.

f. Sweat. Chen and Schmidt determined the sweat secretion of an anesthetized cat and could not detect any increase after ephedrine was injected into the paw. Kreitmair arrived at the same conclusion.

In men a therapeutic dose of ephedrine occasionally produces diaphoresis. It is interesting to note that perspiration caused by the use of Ma Huang, firmly believed in by the Chinese and described by Li Shih-Cheng in his Pentsao Kang Mu, although not experimentally proved in animals, has been clinically confirmed in many reports.

g. Lymph. With the coöperation of M. Kayumi, Chen and Schmidt studied the influence of ephedrine on lymph flow, collected from the thoracic duct of anesthetized dogs. It regularly causes an increase in lymph, which reaches its maximum about 15 minutes after the intravenous injection.

h. Urine. In anesthetized dogs the urine flow appears to follow the plethysmograph of the kidney volume, as observed by Chen and Schmidt. There is suppression during the primary vasoconstriction, but an increase during the secondary dilatation. After repeated doses the urine is invariably suppressed. Intact rabbits which receive daily intravenous injections of ephedrine show a well marked diuresis. Starr, coöperating with T. G. Miller, studied the output of urine in a series of 16 men, in correlation with the systolic blood pressure. He divided his results into three groups: (1) those showing a rise of blood pressure without diuresis and with albuminuria; (2) those showing no rise in pressure with no diminution of urine and no albuminuria; and (3) those showing a rise of pressure with diuresis and albuminuria. The occurrence of albumin in the urine is transitory, for it disappears when the effect of the ephedrine wears off. In those that show an increase in pressure but no diuresis, the albuminuria is due to renal vasoconstriction, while in those that show rise in pressure and increase in urinary output, it is probably due to the alternate constriction and dilitation of the glomerular functional units. Kreitmair observed diuresis on himself after the ingestion of 50 mgm. of ephedrine, lasting for 2 to 3 hours. Gradinescu and Marcu also call attention to the fact that the variation in urine flow depends on vascular changes.

6. Action on the blood

a. Blood cells. Hess reported leucocytosis after ephedrine, reaching its maximum at the same time as the blood pressure attains its highest level. Marcu and Petresco studied the blood changes in men on intravenous injection of ephedrine. A dose of 20 mgm. increases the leucocytes within the first five minutes, lasting for more than one hour and 40 minutes. The leucocytosis consists chiefly of lymphocytosis. The red blood corpuscles are also increased, with a corresponding increase in hemoglobin. The maximum is attained in about 40 minutes. Ephedrine in a dosage of 60 mgm., given intravenously, produces a leucocytosis and erythrocytosis which lasts for two hours or longer. These changes, the authors believe, indicate a concentration of the blood. Pathological conditions apparently modify this reaction. Thus, Marcu and Petresco observed with a dose of 20 mgm. intravenously a decrease of red blood corpuscles and leucopenia in a case of Addison's disease, and leucopenia but erythrocytosis in a case of Hodgkin's disease. Binet, Arnaudet, Fournier and Kaplan observed an increase in platelets in addition to erythrocytosis and leucocytosis in chloralosed dogs. The maximal increase in the platelets is reached at the end of 5 to 15 minutes after the intravenous injection of 3 mgm. of ephedrine per kilogram. According to these investigators the increase in the formed elements of the blood is due to contraction of the spleen, for splenectomy prevents this reaction and previous administration of yohimbine, which paralyzes the contractors of the spleen, abolishes such a response.

b. Blood chemistry. Chen and Schmidt studied the effect of ephedrine on the blood sugar in two anesthetized dogs. Their results were inconclusive. Negative or doubtful results were obtained by T. G. Miller in men, by Hess in men, by Kreitmair in rabbits, by Rudolf and Graham in diabetics, by Tu in men, and by Haintz in men. Hyperglycemia may be produced in animals by doses larger than the pressor ones. Thus, Nagel determined the hyperglycemic dose in rabbits to be 25 mgm. per kilogram, injected intravenously. Wilson found it to be 10 to 15 mgm. per kilogram (intravenously or subcutaneously) in dogs, and 20 to 30 mgm. per kilogram (intravenously) in rabbits. According to Nitzescu, hyperglycemia occurs in dogs when they are in full digestion but is absent when they are previously starved. The doses he used were 0.5 to 3.0 mgm. per kilogram, given intravenously. The simultaneous administration of glucose and ephedrine does not increase the hyperglycemia produced by glucose alone but lengthens its duration. A limited increase in blood sugar in men with therapeutic doses (5 to 100 mgm.) of ephedrine given orally was observed by Pollak and Rabitschek and by Lublin. Radoslav and Stoïcesco administered ephedrine to men by intravenous injection. Doses of 5 to 90 mgm. produce a diphasic reaction—a primary hyperglycemia followed by hypoglycemia. The blood sugar returns to normal in about two hours.

After the intravenous injection of 20 mgm. of ephedrine, the serum albumin increases to the extent of 10 parts per thousand and returns to normal in 20 minutes, while the globulins are increased for two hours, as determined by Marcu and Petresco. The concentration of albumins and globulins occurred in both healthy individuals and in a case of Addison's disease and another of Hodgkin's disease. Unlike epinephrine, ephedrine does not raise the peptidase titer of the rabbit's serum (Pfeiffer and Standenath).

7. *Action on metabolism*

a. Metabolic rate. T. G. Miller reported an increase in metabolic rate in 4 cases with 100 to 125 mgm. of ephedrine injected subcutaneously. Rowntree and Brown also studied the calorigenic effects of ephedrine, given by mouth, in several diseased conditions. In 3 cases of Addison's disease there was an increase in metabolic rate in two but a decrease in the third. In a case of questionable Addison's disease and 4 cases of hypotension, an increase was also demonstrated. The effects seem to be transitory and an hour afterwards there may be a tendency to a fall of metabolic rate. A patient with endocrine obesity showed a decrease of 11 points with 50 mgm., but with 100 mgm. there was an increase of 13 points in 3 hours. In a case of pituitary tumor there was a demonstrable increase of the basal metabolic rate after 50 mgm. of ephedrine had been given. In rabbits, Dulière observed only inconsistent changes in metabolism after the administration of ephedrine.

b. Gaseous exchange. Schmidt (1928) demonstrated that ephedrine increases both cerebral O_2 consumption and CO_2 liberation. Wilson, Pilcher and Harrison, and Halsey, Reynolds and Blackberg also observed an increase in O_2 consumption with a tendency of the alveolar CO_2 to fall. After giving fructose or glucose, the R.Q. is always greater than 1, but if ephedrine and fructose are given at the same time the R.Q. becomes less than 1. According to Lublin, this means the inhibition of fat formation by ephedrine. In rabbits, Dulière constantly observed a decrease of R.Q. following the intravenous injection of ephedrine.

c. Body temperature. With toxic doses Miura in 1887 reported an elevation of temperature in dogs, rabbits and mice. Like epinephrine and β-tetrahydronaphthylamine, ephedrine, according to Hashimoto (1915), slightly raises the body temperature (0.5° to 0.7°C.) in normal rabbits and it produces fever in those animals whose heat centers have been punctured. The dose for the production of this response is 20 mgm. per kilogram. Notwithstanding, Suzuki recently reported a slight fall in rectal temperature in rabbits, either normal, adrenalectomized or with the splanchnic nerves sectioned, using a dose of 30 mgm. per kilogram, given intravenously.

8. Action on the central nervous system

Ephedrine appears to stimulate the central nervous system. Airila in 1913 showed that chloralized rabbits can be awakened temporarily by an intravenous injection of ephedrine (10 to 20 mgm.). Morita in 1915 obtained similar results in rabbits whose cerebral hemispheres had been removed, and believes that the stimulation is subcortical. In the squid, *Loligo pealii*, doses of 5 mgm. or more make it turn blood-red within half an hour, the color persisting for twelve to twenty hours or more, as observed by Nadler. Oral administration and injection into the circulation via the heart likewise produce this dark coloration. The author attributes this change to stimulation of the central nervous system. In men moderate doses of ephedrine sometimes cause tremor, nausea, and insomnia, which in all probability is due to stimulation of the central nervous system. C. F. Schmidt obtained evidence that ephedrine directly stimulates the respiratory center. In anesthetized dogs, Johnson and Luckhardt found that ephedrine in large doses, injected intravenously or subcutaneously, causes a marked increase in the reflex excitability of the spinal cord, as measured by the knee jerk. The action is not dependent on any influence of the higher centers on the cord nor due to the hemodynamic action of the drug, since the increase in excitability of the cord outlasts the rise of blood pressure.

9. Action on the peripheral nerves and voluntary muscles

The action of ephedrine on the motor nerves has been studied by Read and Lin. They conclude that ephedrine potentiates the action of novocaine on the frog's sciatic nerve. By the addition of 0.005 per cent of ephedrine to a 1 per cent solution of novocaine the time required for blocking of the motor impulse is lessened by 80 per cent.

Ogata (1920) states that ephedrine has no local anesthetic action, meaning that it is devoid of action on the sensory nerve endings. Read and Lin, on the other hand, claim that a mixture of ephedrine with epinephrine and potassium sulphate can produce, by the wheal method, local anesthesia equal in intensity to that produced by a mixture of similar proportions and strengths of novocaine, epinephrine and potassium sulphate.

Amatsu and Kubota (1917) studied the effect of ephedrine on the frog's gastrocnemius muscle. They found that a 0.1 per cent solution raises the threshold of stimulation (electric) and produces irregular contractions on repeated stimulation with a current of constant strength, instead of a gradual fatigue curve.

10. Mode of action

In a previous review of this subject, Chen and Schmidt (1926) divided the actions of ephedrine into three categories: the therapeutically useful ones, which are due to peripheral sympathomimetic effects; the stimulant action upon the central nervous system; and the depressant action upon heart muscle. The second and third types of action were said to be exerted as a rule only by excessive dosage and were regarded as undesirable or dangerous. Subsequent developments have necessitated a modification in this characterization in so far as the central nervous effects are concerned, for it is now certain that they may be elicited by therapeutic doses in some individuals at least, and may be useful in combating the action of narcotic poisons, particularly upon the respiratory center. The action of ephedrine upon the brain cells has not been analyzed, but it appears to be comparable with that of caffeine (Schmidt, 1928). The depressant action upon heart muscle is essentially similar to that of any other myocardial depressant, and the only practical importance of this type of effect is that it imposes limitations upon the therapeutic usefulness of the drug. There is no disagreement among various workers with respect to the central nervous and myocardial depressant effects of ephedrine.

The peripheral actions of ephedrine, which are of greatest interest to the clinician, are not so simply disposed of. The earliest workers in this field (Amatsu and Kubota, 1917; To, 1921; Chen and Schmidt, 1924) were impressed with the obvious similarity of the effects of ephedrine to those of epinephrine, and concluded that ephedrine is a sympathomimetic substance. These effects include mydriasis with preservation of light and accommodation reflexes, broncho-dilatation, cardiac acceleration and augmentation, vasoconstriction, inhibition of gastro-intestinal motility (in many cases), hyperglycemia, and occasional secretion of saliva by the atropinized submaxillary gland. In fact no other explanation is possible for these effects, taken as a whole. The question is not whether ephedrine produces sympathomimetic effects but whether its important effects are due wholly or even largely to such actions. During recent years considerable evidence having been obtained, by a number of investigators, that the peripheral effects of ephedrine differ qualitatively in some respects from those of epinephrine, the conclusion has been drawn that ephedrine owes some of its effects to direct excitation of smooth muscle, irrespective of sympathetic innervation. Those who have concluded that ephedrine acts at least partly upon muscle fibers include Nagel (1925), De Eds (1927), De Eds and Butt (1927), Pak and Read (1928), Méhes and Kokas (1929), and Halsey (1928). The question has more than theoretical importance, for if this conclusion is fully justified ephedrine should be looked upon as a drug with the clinical usefulness of pituitrin rather than that of epinephrine.

Decisive evidence upon a point of such fundamental importance as this might well be sought in investigations of the action of the drug upon simple organisms or preparations. The only pertinent investigation of the action of ephedrine upon a lower form of life is that of Nadler (1927), which has already been discussed (page 16). He concluded that ephedrine is essentially sympathomimetic, not musculotropic. However, the organism used by him is relatively complex, and the exact mechanism of the responses studied has not been established. The results seem to the reviewers to be suggestive but not conclusive evidence upon the point at issue.

A relatively uncomplicated preparation of mammalian tissue is the plexus-free strip of small intestine of the cat (Gasser: Journ. Pharmacol. Exper. Therap., 1926, xxvii, 395). This apparently has not been used to test the musculotropic power of ephedrine. One of the reviewers (S.) recently tested 12 such preparations with ephedrine. In no case was there any trace of stimulation, and depression was more commonly observed with ephedrine than with epinephrine. The number of observations was small, but all the preparations were active, and it is reasonable to suppose that a conspicuous musculotropic action would have been disclosed if present. These results lend no support to the conception that ephedrine is musculotropic. In fact they suggest rather that the direct action of ephedrine upon smooth muscle is a depressant one, since ephedrine was more uniformly inhibitory than epinephrine.

Another suitable test-object would be blood vessels which are not conspicuously affected by epinephrine, such as those of the coronary, cerebral, and pulmonary areas. The only available information concerning the action of ephedrine upon such structures is the statement of Chen and Schmidt (1924) that coronary outflow from the perfused mammalian heart was augmented, never decreased, by ephedrine. This is far from conclusive evidence upon the point at issue, since rate and force of cardiac contractions were also increased. However, pituitrin regularly causes very marked reduction in coronary flow in such preparations. If the latter is regarded as a representative example of the effect of musculotropic agents, the result with ephedrine indicates that the latter is not musculotropic. Further information concerning the actions of ephedrine upon coronary, cerebral, and pulmonary vessels is highly desirable.

The contention that ephedrine is capable of exerting stimulant effects upon smooth muscle fibers irrespective of their innervation is based upon observations of two general sorts. These are, the influence of certain other substances (ergotoxine, yohimbine, cocaine, insulin) upon the circulatory effects of ephedrine, and the action of ephedrine upon various preparations of isolated smooth muscle. None of the evidence so far obtained by these procedures appears to be decisive.

a. Circulatory responses. The fact that ergotoxine (ergotamine) leads to a reversal of the blood pressure effect of epinephrine has led to the employment of ergotoxine as a means of discriminating between sympathomimetic and musculotropic effects on the part of other drugs which raise blood pressure. Other things being equal, a given quantity of the agent being tested should cause a fall in pressure after ergotoxine if it is sympathomimetic, while if its effects are unaltered by ergotoxine it must be musculotropic.

Among those who have tested the influence of ergotoxine upon the pressor response to ephedrine are Nagel (1925), Kreitmair (1927), De Eds and Butt (1927), Chen (1928), and Curtis (1929). All found that the pressor effect of ephedrine was reduced by ergotoxine, but Curtis was the only one who reported complete absence of such effect or an actual reversal after ergotoxine, though a reversal of epinephrine effects was clearly demonstrated in every case. Curtis attributed his success to the use of smaller quantities of ephedrine and larger doses of ergotoxine than had been used by his predecessors. Until this is confirmed, however, it appears proper to conclude that while ergotoxine may diminish or even prevent the pressor effect of ephedrine, an actual reversal, similar to that of epinephrine, is not the characteristic result.

These results have been interpreted as strong evidence in favor of a musculotropic action by ephedrine, but such conclusion is by no means obligatory, for two reasons: First, as has been emphasized repeatedly (Chen and Schmidt 1924, 1926; Chen and Meek, 1926; Chen, 1928; Curtis, 1928), the pressor effect of ephedrine is due more to increased cardiac action than to vasoconstriction, while in the case of epinephrine the reverse is true. It is well known that ergotoxine, in quantity sufficient to paralyze vasoconstrictor receptors and therefore to produce the epinephrine reversal, has much less effect upon the cardiac accelerator system (see Chen, 1928). It is through the latter system that ephedrine exerts much of its influence upon blood pressure. Consequently one need not expect the pressor effect of ephedrine to be abolished by ergotoxine until the latter is present in sufficient quantity to paralyze the cardiac accelerator system, and Curtis (1928) states that with sufficiently large doses of ergotoxine the pressor effect of ephedrine can be completely prevented. These objections to the conclusions derived from the ergotoxine experiments have been raised by Chen (1928) and by Curtis (1928).

Second, it must be remembered that the epinephrine reversal by means of ergotoxine presupposes a powerful stimulant action by epinephrine upon vasodilator nerves, but there is no reason to believe that ephedrine possesses such an action. For, as has already been pointed out (page 20), the smallest effective doses of ephedrine produce only a rise in blood pressure, and as the effects of ephedrine wear away blood pressure returns to normal, not to a subnormal level. One of the outstanding advantages of ephedrine over epinephrine as a constrictor of nasal blood vessels is the absence of after-dilatation in the case of ephedrine. There is no decisive evidence upon this point, but these observations suggest strongly that the effects of ephedrine upon blood vessels are dominantly if not exclusively motor (constrictor), while in the case of epinephrine inhibitory (dilator) actions are conspicuous (Dale, 1906). The present situation is therefore practically identical with that encountered by Barger and Dale (1910) in their investigation of sympathomimetic bases. They found that ergotoxine reduced but did not reverse the pressor effect of amino-aceto-catechol or *dl*-amino-ethanol-catechol, while it led to complete reversal of the effects of methylamino-catechol or *dl*-epinephrine. The difference was attributed to a greater predominance of inhibitory (vasodilator) actions on the part of the latter substances, though the effects of all were regarded as purely sympathomimetic. The failure of ephedrine to produce a fall in blood pressure after ergotoxine cannot therefore be regarded as proof that ephedrine is not sympathomimetic.

The above considerations probably apply also to the effects of yohimbine, which Raymond-Hamet (1927) found to exert an influence like that of ergotoxine: the pressor response to epinephrine was inverted, while that to ephedrine was only reduced.

Cocaine is another agent which has been used to determine whether a pressor drug is sympathomimetic or musculotropic, as a result of the work of Tainter and Chang (1927). They found that a small dose of cocaine augmented the pressor effect of epinephrine, but reduced or abolished that of tyramine, the latter being regarded as musculotropic. De Eds (1927) and Pak and Read (1928) found that cocaine also reduced the pressor effect of ephedrine. Chen (1928) was unable to confirm this conclusion; he believed that the result was due simply to the fact that a second dose of ephedrine is less effective than the first even if no cocaine is given between them. However, Tainter (1929) has recently shown that cocaine, in dosage which augments the pressor effect of epinephrine, may reduce or abolish that of ephedrine.

These results have been interpreted as evidence that ephedrine is not sympathomimetic, but musculotropic, in its circulatory effects.

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Yet, as far as the reviewers are aware, no evidence has been presented that cocaine augments the effectiveness of sympathetic nerve excitation by anything but epinephrine, and this particular effect might well be a drug synergism, peculiar to epinephrine, with no relation to sympathetic stimulation *per se.* Nor is there any evidence that reduction of pressor effectiveness by cocaine is an index of musculotropic action. In fact Tainter has recently reported (XIII International Physiological Congress) that cocaine neither increases nor decreases the effectiveness of barium and pituitrin. If one grants the validity of the assumption that any agent, to be sympathomimetic, must duplicate all of the peculiar effects of epinephrine, the cocaine test, like the ergotoxine one, indicates that ephedrine is neither sympathomimetic nor musculotropic.

Another agent which modifies the circulatory response to epinephrine much more than that to ephedrine is insulin. Csépai and Pinter-Kováts (1927) found that insulin prevents the pressor effect of epinephrine, but not that of ephedrine. The significance of this observation, apart from an indication that the circulatory effects of ephedrine are in some way different from those of epinephrine, is unknown to the reviewers.

It seems to the reviewers that these various circulatory responses, in the present state of our knowledge, can show only whether a substance does or does not elicit certain effects that are characteristic of epinephrine. If they are to be used for the purpose of determining whether a new drug is or is not likely to be of practical value as a substitute for epinephrine, one must consider the fact that ephedrine, which, according to all these tests, is not epinephrine-like, has amply proved its practical value as a substitute for epinephrine. The reviewers do not believe, therefore, that absence of epinephrine-like responses in the ergotized or cocainized animal can be regarded as convincing evidence of lack of sympathomimetic action on the part of other substances.

b. Effects upon smooth muscle. In considering the work that has been done upon this subject (pages 33–40) it was pointed out that the effects of ephedrine upon uterus and bladder fundus appear to be uniformly stimulant, though epinephrine may be depressant; that the surviving small intestine may be stimulated or depressed by ephedrine though invariably depressed by epinephrine. Apparently the only smooth muscles that are uniformly relaxed in vitro by ephedrine are found in the bronchi, the sphincter pupillae and the uterus of the albino rat. While it is somewhat difficult to see why a substance which acts directly upon smooth muscle fibers should stimulate some and depress others, it is equally difficult to see why a substance which owes its effects to sympathomimetic actions should so frequently lead to contraction of structures that are relaxed by epinephrine.

Considering first the isolated small intestine, however, a reason for this discrepancy is readily found in an action by ephedrine upon motor ganglia as well as inhibitory endings. Chen and Schmidt (1924, fig. 5) showed a tracing which illustrated the epinephrine-like effect of ephedrine after the ganglia had been paralyzed with nicotine. This procedure has recently been repeated by one of the reviewers (S.) with preparations made from the small intestines of cats, dogs, and rabbits, and the results have been uniformly like the earlier ones. In no instance did ephedrine fail to exert a typical sympathomimetic effect after nicotine, while stimulation of strips from adjacent parts of the bowel was frequently observed when ephedrine was applied before nicotine. Reference has also been made (page 47) to the uniform absence of stimulant effect by ephedrine upon plexus-free preparations of small intestine. It appears, therefore, that the intestinal effects of ephedrine consist in a combined stimulation of ganglia (plexus of Auerbach), which causes increased motility, and of inhibitory sympathetic endings. When the ganglionic action is excluded by means of nicotine or removal of the plexus, the sympathomimetic action is clearly and uniformly manifested.

In the case of the uterus, the corresponding information is not available. Ephedrine is almost invariably stimulant to isolated uteri, whether epinephrine is stimulant or inhibitory, and this argues in favor of the musculotropic or pituitrin type of effect. Ergotoxine has been added to the solution in which the uterus was immersed, by Nagel (1925), Kreitmair (1927), De Eds and Butt (1927), Reinitz (1928), and Curtis (1929). This substance should paralyze motor sympathetic nerve endings, and uteri so treated were uniformly inhibited by epinephrine, but all observers except Curtis reported that ergotoxine did not prevent the stimulant action of ephedrine: he stated that by means of large doses of ergotoxine the effects of ephedrine could be prevented though never reversed. It may be, therefore, that the effects of ephedrine upon the isolated uterus are indeed sympathomimetic, but are exerted mainly if not exclusively upon motor parts of the system, the inhibitory parts being affected much less or not at all—an analogy to the effects upon blood vessels.

The stimulant action of ephedrine upon the intestine being apparently similar to that of nicotine (i.e., ganglionic), a similar action upon the uterus may be regarded as a possibility. This has not been investigated. It is not possible at present to make a plexus-free preparation of uterine muscle. The effects of nicotine upon the uterus (virgin organ of the cat) were found by Barger and Dale (1910) to be inhibitory in vivo but stimulant in vitro. In current terminology, this would imply that nicotine is sympathomimetic in vivo, musculotropic in vitro. Barger and Dale, however, believed that the inhibitory effect in vivo was due to stimulation of sympathetic ganglia which rapidly lose their sensitivity when the uterus is excised. They did not explain the stimulant action in vitro, but it can scarcely be called musculotropic because nicotine does not stimulate ganglion-free smooth muscle of the intestine (Gasser, 1926).

The situation appears to be rather obscure, and the reviewers believe that the true explanation of the uterine effects of ephedrine can be given only when more is known about the intrinsic innervation of the organ.

The situation with respect to the urinary bladder muscle is much the same. The only data are those of Macht (1929) and Liljestrand (1927) (see page 40, above). These effects of ephedrine are like those of pituitrin, unlike those of epinephrine. The results are equivocal evidence for or against a musculotropic action by a drug that appears to affect certain ganglia as well as endings, and to stimulate motor sympathetic nerves more powerfully than inhibitory ones.

It has been claimed by Fujii (1925), Kreitmair (1927), Reinitz (1928), and Marcu and Savulesco (1928) that ephedrine stimulates both parasympathetic and sympathetic nervous systems, but the evidence presented in support of this contention is inconclusive. Fujii (1925) believed that the constrictor action of ephedrine upon perfused blood vessels of the frog was exerted through parasympathetic nerve structures, since it was absent when atropine was added to the perfusion fluid; however, it is well known that atropine has a vasodilator action of its own in such circumstances (Cushny, Textbook of Pharmacology, 1928, p. 347). Fujii, as well as Reinitz (1928), found that atropine prevented the stimulant action of ephedrine upon the isolated uterus, but this has not been the case in the experience of the reviewers. Kreitmair (1927) reported that the stimulant action of ephedrine upon isolated intestine was prevented or abolished by atropine, but this is denied by Reinitz (1928). Méhes and Kokas (1929) claim that atropine partly prevents the depressant action of ephedrine upon the perfused frog's heart, but this is opposed to the results of Fujii (1925) and Kreitmair (1927).

Apparently there is no better agreement concerning the preferential action of ephedrine, assuming that it acts upon both nervous systems. Kreitmair (1927) believed that minimal doses affected only the sympathetic, and that the parasympathetic was influenced only by relatively high concentrations. Marcu and Savulesco (1928), however, claim that minimal quantities stimulate the parasympathetic preferentially, while with large doses sympathetic stimulation dominates the picture, the effects of intermediate dosages being antagonistic and therefore inconstant or absent.

Further work is needed before this point can finally be settled. The conflicting opinions indicate that ephedrine certainly has no conspicuous pilocarpine-like effects, and Reinitz (1928) claimed that it actually has an atropine-like effect upon the intestine. There is no reason therefore for employing ephedrine as a parasympathetic stimulant.

As to the exact site of ephedrine actions, there is little information. Chen and Schmidt (1924) pointed out that ephedrine was able to dilate the pupil whose sympathetic (pupillo-dilator) innervation had degenerated following extirpation of the ganglion, while cocaine was ineffective. They concluded that the point of action of ephedrine was apparently peripheral to that of cocaine, the absence of effect from the latter indicating degeneration of the structures upon which it acted. Marcu and Gheorghiu (1927) have recently shown that ephedrine is able to increase the rate of a heart whose accelerator nerves have degenerated following removal of the ganglia: this also points to an action upon structures peripheral to the finest nerve fibrils, which degenerate when the ganglion is removed. On the other hand, there is no good reason to attribute any of the peripheral effects of ephedrine to direct action upon effector substance (muscle fibers, gland cells). This makes the situation comparable to that encountered with epinephrine, and leads to the conclusion that ephedrine likewise acts upon hypothetical myoneural junctions.

However, there is reason to believe that the myoneural junctions affected by ephedrine are not the same as those affected by epinephrine, in the pupillo-dilator system at least. Reference has already been made (page 34) to a few observations which indicate that denervation does not sensitize the pupil to ephedrine, but diminishes its effectiveness. Should this be confirmed, it would suggest that some of the ephedrine receptors degenerate after denervation, as all of those for cocaine appear to do. This would imply that the point of action of ephedrine upon the pupil is at least partly central to that of epinephrine, and partly peripheral to that of cocaine.

It has been suggested by several workers that many of the peculiarities in the action of ephedrine could be explained on the basis of an increased secretion of epinephrine by the suprarenal glands as a result of absorption of ephedrine. This would account for the effects of ephedrine upon metabolism, blood sugar, etc. and for epinephrine-like effects upon small intestines in situ, not in vitro. The question has a practical significance in connection with the treatment of Addison's disease.

Evidence upon this point is somewhat contradictory. Nagel (1925) reported that suprarenalectomy did not reduce, but seemed to augment the pressor effectiveness of ephedrine. Chen and Schmidt (1926) stated that removal or ligation of the suprarenal glands did not diminish the pressor effect of ephedrine. It seems clear, therefore, that the circulatory effects of ephedrine are not due wholly to stimulation of the suprarenal glands.

On the other side, Suzuki (1928) found that a given dose of ephedrine produced a smaller and briefer rise in blood pressure in unanesthetized rabbits whose splanchnic nerves had been cut or whose suprarenal glands had been removed, than it did in normal controls. Section of the splanchnics reduced the effectiveness of ephedrine more than suprarenalectomy did, which suggests that part of the influence of ephedrine upon the suprarenals must be exerted through the nervous system. Gradinesco and Marcu (1927) found that a small quantity (0.1 to 0.2 cc. of a 1 per cent solution) of ephedrine, injected directly into the suprarenal capsules of dogs anesthetized with chloroform, caused a marked and sustained rise in blood pressure. To reproduce the effect by intravenous injection of ephedrine, 7 to 10 times the quantity was required. They reported also that removal of the suprarenals led to marked reduction in the pressor effectiveness of ephedrine, which is opposed to the results reported by Nagel (1925) and by Chen and Schmidt (1926). Houssay and Molinelli (1927) employed a crossed-circulation (suprarenalo-jugular anastomosis) preparation in dogs. They reported that large doses (40 to 50 mgm. per kilogram) of ephedrine caused increased suprarenal output in six out of ten attempts. The effect was abolished by section of the splanchnic nerves, and was therefore presumably due to an action upon the nervous system—a conclusion which is like that of Suzuki (1928). It must be noted, however, that the doses of ephedrine used by Suzuki (30 mgm. per kilogram) and by Houssay and Molinelli (40 to 50 mgm. per kilogram) are so close to the toxic level that nervous effects are to be expected. Only the results of Gradinesco and Marcu point to the possibility of a suprarenal stimulation by small quantities of ephedrine, and these could scarcely be regarded as small when they were injected directly into the gland.

It appears that ephedrine is probably capable of stimulating the suprarenal glands, but whether the effect can be elicited by ordinary doses or is exerted only by toxic quantities has not been determined. It is certain that an action of this sort cannot account for all of the effects of ephedrine, for some of these are elicited upon local application (pupil), others are demonstrable in excised tissues (heart, perfused blood vessels, isolated smooth muscle). Clinical experience has shown that ephedrine has no beneficial influence upon the course of Addison's disease. However, since the pathological process is a progressive one which ephedrine could not be expected to check, this does not prove that the drug had not stimulated the residual normal tissue.

The above discussion concerning the mode of action of ephedrine can be summarized as follows:

There is no valid evidence that ephedrine is capable of directly stimulating any smooth muscle, while there is some direct evidence that it cannot do so (chromatophores of the squid, plexus-free and nicotinized intestine, albino rat uterus).

There is reason to suspect that ephedrine stimulates motor sympathetic nerves more powerfully than inhibitory ones when both are present in the same tissue (blood vessels, perhaps uterus and bladder), and possibly the inhibitory set is not affected at all by ephedrine; but when the sympathetic innervation is purely inhibitory ephedrine seems uniformly to stimulate it (bronchi, isolated sphincter pupillae, isolated intestine—nicotinized, plexus-free, sometimes intact).

Ephedrine appears to stimulate certain ganglia (cardiac accelerator, plexus of Auerbach), but whether this is a general effect or is limited to these localities has not been determined.

Its peripheral effects have not been shown definitely to involve the parasympathetic system, unless the plexus of Auerbach is regarded as a part of the latter. Ephedrine certainly has no conspicuous pilocarpine-like actions, and its important effects are not prevented by atropine.

There is no conclusive evidence that ordinary therapeutic doses of ephedrine stimulate the suprarenal gland, or that any of the effects of such doses are so caused.

The point of action of ephedrine upon the pupil appears to be central to that of epinephrine, peripheral to that of cocaine, i.e., peripheral to the finest anatomically demonstrable nerve fibers.

As to the precise mode of action, one can, in the present state of our knowledge, only characterize it by one of two general, descriptive terms—sympathomimetic or musculotropic. The first, according to the definition of Barger and Dale (1910), who introduced it, implies that the effects of the drug are analogous to those of excitation of the sympathetic nervous system by other agencies, such as electrical stimulation. The second is currently used to designate a group of drugs and poisons which stimulate smooth muscle indiscriminately and irrespective of its innervation. The outstanding example of the first group is epinephrine, while of the second pituitrin and barium are representative. In the recent investigations of ephedrine it has been tacitly assumed that epinephrine actions are the absolute standard of sympathomimetic effects. But the originators of the term (Barger and Dale, 1910) pointed out that in some respects the effects of epinephrine are unlike those of electrical excitation of the sympathetic as well as those of many sympathomimetic drugs, notably in the pronounced tendency of epinephrine to produce inhibitory effects upon blood vessels and uterus of the cat. It does not seem to the reviewers that, with such observations on record, it is necessary to restrict the group of sympathomimetic agents to those which duplicate the actions of epinephrine in all respects.

Clasification of ephedrine in one or the other of these categories is at present rather arbitrary, for the choice depends upon the definition of the terms. Since neither term is explanatory of the mode of reaction of drug with tissue substance, but is merely descriptive of observed or expected phenomena, the choice is of no great immediate importance. However, the reviewers believe that it is better at present to regard ephedrine as sympathomimetic in all its peripheral effects than to consider it as sympathomimetic in some localities, musculotropic in others. This choice is based partly upon the burden of clinical evidence, which justifies the retention of ephedrine as a drug with the general usefulness of epinephrine, and partly upon the possibility of future developments. If stimulation by ephedrine of structures that are depressed by epinephrine is conclusive proof that ephedrine is musculotropic, the matter is closed, and little or nothing has been added by way of fundamental knowledge to utilize in investigation of other substances. But if search is made for an explanation of these discrepancies upon a sympathomimetic basis, it is reasonable to suppose that something will be added to our knowledge concerning the sympathetic innervation of various structures, and it is not inconceivable that progress may be made toward an explanation of the extraordinary predilection of many substances for the sympathetic nervous system, or for certain parts of it.

It is quite possible that some of the effects of ephedrine are musculotropic. The facts remain, however, that no valid evidence exists that such is the case, that at least one of the supposedly musculotropic actions can even now be shown not to be such (i.e., the stimulant effect upon isolated intestine), and that the general picture of ephedrine actions is strikingly similar to that resulting from stimulation of the sympathetic nervous system by other means. The reviewers therefore believe it proper to await unequivocal demonstration of musculotropic actions by ephedrine, and the exclusion of the possibility of sympathetic stimulation as an explanation, before accepting the view that any of the peripheral effects of ephedrine are not sympathomimetic.

11. Absorption and excretion

Ephedrine is readily absorbed and produces systemic effects when administered orally, subcutaneously, intramuscularly, subdurally, intraperitoneally, or rectally in animals, and the same has been shown to be true of men excepting for the subdural and intraperitoneal routes, which have not been tried. The rate of absorption in men, evidenced by the rise in blood pressure, is somewhat faster following subcutaneous or intramuscular injection than following oral administration, but the degree of effect is not significantly different (Miller, 1925); evidently absorption from the alimentary tract is complete. The effects of intravenous injection are much briefer than those of other modes of administration (Jansen). The readiness with which ephedrine is absorbed represents an outstanding and usually advantageous difference from epinephrine; it may be due to a lack of constrictor action of ephedrine upon finer blood vessels.

The fate of ephedrine in the body is still unknown, for there is no reliable and sensitive method for detecting it in tissues or excreta. It apparently passes through the liver unchanged but whether it is destroyed in the body or eliminated, in unaltered or altered form, is unknown, nor is anything known about the route of elimination.

12. Toxicity

a. Minimal lethal dose. Table 2 shows the toxicity of ephedrine in different animals. The order of the M.L.D. by different methods of administration is as follows: intravenous, intramuscular, intraperitoneal, subcutaneous, and oral. The drug is therefore most toxic by intravenous injection and least toxic by mouth. In general, different workers agree that ephedrine has a low toxicity and a wide margin of safety. In dogs, for example, the optimal pressor dose intravenously is 1 to 10 mgm. per kilogram while the M.L.D. by the same

TABLE 2

Toxicity of ephedrine in different animals

ANIMAL	EPHEDRINE	METHOD OF ADMINISTRATION	M.L.D.	AUTHOR
			mgm. per kgm.	
Squid (*Loligo pealii*)	Sulphate	Subcutaneous	10*	Nadler
Frog	Hydrochloride	Subcutaneous	400–500	Amatsu and Kubota
	Hydrochloride	Subcutaneous	440	Fujii
	Hydrochloride	Subcutaneous	600	Kreitmair
	Hydrochloride	Subcutaneous	540	Pak and Read
	Sulphate	Subcutaneous	530–690	Chen
Hamster	Hydrochloride	Intraperitoneal	350	Pak and Read
Mouse	Hydrochloride	Subcutaneous	500	Fujii
	Hydrochloride	Subcutaneous	1,000	Kreitmair
	Hydrochloride	Oral	3,000	Kreitmair
	Hydrochloride	Intravenous	200	Kreitmair
White mouse	Sulphate	Intraperitoneal	400	Rowe
Rat	Hydrochloride	Subcutaneous	320	Pak and Read
White rat	Sulphate	Intravenous	135–140	Chen
Guinea pig	Hydrochloride	Subcutaneous	400	Kreitmair
	Sulphate	Subcutaneous	400–425	Chen
Rabbit	Hydrochloride	Subcutaneous	300–460	Miura
	Hydrochloride	Subcutaneous	400–500	Amatsu and Kubota
	Hydrochloride	Intravenous	50	Kreitmair
White rabbit	Hydrochloride	Intravenous	50	Pak and Read
	Hydrochloride	Intravenous	60	Chen
	Sulphate	Oral	590	Chen
	Sulphate	Subcutaneous	320–400	Chen
	Sulphate	Intraperitoneal	310–400	Chen
	Sulphate	Intramuscular	340	Chen
	Sulphate	Intravenous	66–70	Chen
Gray rabbit	Hydrochloride	Subcutaneous	230	Pak and Read
	Hydrochloride	Intravenous	80	Pak and Read
Cat	Hydrochloride	Intravenous	60	Kreitmair
	Sulphate	Intravenous	75	Chen
Dog	Hydrochloride	Subcutaneous	220	Miura
	Hydrochloride	Intravenous	70	Pak and Read
	Sulphate	Intravenous	70–75	Chen

* Total dose.

route of administration is 70 to 75 mgm. per kilogram. It is interesting to note the great deviation of the M.L.D. in mice obtained by Kreitmair from those reported by Fujii and by Rowe. The difference by subcutaneous injection is fully 100 per cent or more. One wonders if these three workers experimented on the same species of animals. The variations in the results, not more than 10 to 20 per cent among other investigators, should not be considered significant if one bears in mind the errors in the determination of toxicity. Such errors have been critically analyzed by Trevan (Proc. Roy. Soc., 1927, B, ci, 483) and by Burn (Methods of Biological Assay, London, 1928).

b. Toxic symptomatology. Miura (1887) briefly described the toxic signs in animals with lethal doses of ephedrine. He observed general depression, mydriasis, stoppage of the respiration and diastolic standstill of the heart in frogs. The signs of poisoning in mice, rabbits and dogs, as stated by him, are mydriasis, elevation of temperature, acceleration of the pulse and respiratory rates, fall of blood pressure, clonic convulsions and death due to cardiac and respiratory failure. Amatsu and Kubota (1913) reported about the same results. More detailed investigations were carried out by Chen on frogs, rats, guinea pigs, rabbits, cats and dogs. In his experience, cardiac collapse occurs sooner than respiratory failure. Animals poisoned by sublethal doses of ephedrine recover without complications. A full account of poisoning symptoms in frogs, mice, guinea pigs, rabbits and cats is also given by Kreitmair.

The picture in the squid, described by Nadler, may be worth mentioning. Ten milligrams of ephedrine given subcutaneously frequently cause gangrene and necrosis at the site of injection, leaving the muscles of the mantle exposed. The animal may, however, live for hours. Oral administration and injection into the circulation via the heart, in 5 to 10 mgm. dosage, produce a dark coloration. In these cases the arms are extended and limp, and on stimulation they go into a series of tonic contractions. The respiratory movements are faster and heavier, gradually become slower and labored, and death occurs.

c. Repeated administration. In a series of rabbits Chen gave daily doses of ephedrine for several weeks intravenously, intramuscularly and orally and reported that the drug produces no observable toxic effects. These animals gained in weight as steadily as the controls. Upon sacrifice, there were no gross or microscopic lesions in the visceral organs. No tolerance is developed to the mydriatic or pressor action of ephedrine by repeated administration, nor is there any change in the dose required to cause death. Similar results were obtained in rats. This work has recently been verified by Doty.

IV. CLINICAL APPLICATIONS

1. Methods of Administration and Dosage

For systemic effects, ephedrine can be given by mouth, by subcutaneous or intramuscular injection, and only exceptionally by intravenous administration. On occasion, the drug may be used per rectum, as shown by Thomas and by Hess. For local application to the nasal mucous membrane, concentrations varying from 1 to 5 per cent can be used. It may be in the form of a solution, pure or mixed with other aromatic ingredients, a jelly or a snuff. As a mydriatic, ephedrine is used in 5 to 10 per cent aqueous solutions.

As regards the dosage for internal administration, this is governed entirely by the development of untoward symptoms. A small dose for one individual may be a large one for another. From the experience of early investigators, a single dose may be 50 to 100 mgm. for an average adult. Hess advocates the use of 1 to 2 mgm. per kilogram of body weight. This dose appears to be slightly too large, especially for ambulatory patients, judging from the frequent occurrence of side reactions. It has now been reduced to 25 to 50 mgm., and may be repeated as needed. It can be given three or four times a day.

In children from 2 to 14 years of age, Munns and Aldrich use 12 to 50 mgm. of ephedrine by mouth. Anderson and Homan employ $\frac{1}{4}$ grain (15 mgm.) for those over 1 year of age and $\frac{1}{8}$ grain (7.5 mgm.) for those under 1 year, the drug being given in water solution. Stewart prescribes $\frac{1}{6}$ grain (10 mgm.) in children from 1 to 5 years, $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mgm.) from 5 to 6 years, $\frac{1}{8}$ grain (7.5 mgm.) from 6 to 12 months, and $\frac{1}{12}$ grain (5 mgm.) under 6 months of age. Such doses are given with 20 minims of glycerine and enough chloroform water to make a dram (4 cc.).

2. Side effects

The untoward symptoms of ephedrine, given orally, subcutaneously or intramuscularly, have been recorded by T. G. Miller, Rowntree and Brown, Gaarde and Maytum, Pollak and Robitschek, MacDermott, Hollingsworth, Thomas, Balyeat, Berger and Ebster, Althausen and Schumacher, Wu and Read, Anderson and Homan, Kesten, Middleton and Chen, Wilmer, Gay and Herman, Bloedorn and Dickens, Boston, Long, Ségard, Chopra, Dikshit and Pillai, Higgins, and Stewart in connection with their clinical investigations. The development of such symptoms and signs depends upon the dosage but more upon the stability of the nervous system, as emphasized by Pollak and Rabitschek. Similarly, Gaarde and Maytum state that the occurrence of the nervous smptoms bears a distinct relationship to a neurotic tendency and the daily activity of the individual. The same therapeutic dose, therefore, may produce only desirable effects in one patient, and equally beneficial results but with some discomfort, in another. Meals sometimes aggravate the symptoms (Middleton and Chen). It is the best plan to test out the sensitivity of the patient with small doses, say 10 mgm., and establish the maximal tolerated dose. It is only by experience and judgment that these side reactions can be reduced to a minimum.

Subjectively, the common symptoms are palpitations, trembling, weakness, sweating, feeling of warmth, chilly sensation, nausea, and vomiting, while those of less frequent and rare occurrence are nervousness, headache, insomnia, dyspnea, a tired feeling, thirst, drowsiness, precordial pain, feeling of distress in the precordium, flushing of the skin, tingling and numbness of the extremities, anorexia, constipation, quivering feeling, faintness and diuresis. Boston makes a special report of difficulty in urination in 6 cases he observed. Berger and Ebster give an account of a neurotic patient who had colic, followed by diarrhea and anorexia, after the use of ephedrine, and of still another who had such an increase of libido that he called ephedrine an aphrodisiac. Higgins reports a case of chronic ephedrine poisoning which simulated hyperthyroidism.

Objectively, the common signs are diaphoresis, tremor, extrasystoles and tonal arrhythmia, while those of less frequent or rare occurrence are tachycardia, restlessness, mydriasis, albuminuria, appearance of red blood corpuscles and casts in the urine, and decompensation in organic cardiac disorders. Anderson and Homan observed abdominal distension, pain and discomfort, discharge from the nose and apparent suppression of urine. T. G. Miller recorded a case of myocardial degeneration in which ephedrine caused pulsus alternans. Four out of 11 cases in the series of Middleton and Chen showed after ephedrine extrasystoles of ventricular or auricular origin, as shown by electrocardiography. Another case developed a paroxysm of tachycardia which lasted for a few minutes. Bloedorn and Dickens describe a case of cardiac asthma, diagnosed as bronchial asthma, which resulted in cardiac embarrassment, including pulsus alternans, marked tachycardia and cardiac decompensation, following ephedrine therapy. Such dangerous effects, however, do not appear to occur very frequently, for in the series of Hess and of Gay and Herman there were several patients with myocardial insufficiency but none experienced any harmful effects. Pennetti observed, by means of electrocardiograms, that ephedrine increased the frequency of pre-existing extrasystoles in 2 cases but produced no change in a case of A-V block of vagal origin. The block in the last case disappeared after the administration of atropine or epinephrine.

All the side effects occur singly or in groups of but a few, become most pronounced when the systolic blood pressure is at its highest level, and disappear as the pressure returns to normal. Some of the subjective symptoms may be explained by the pharmacological action of the drug. For example, palpitation is due to circulatory changes, as borne out by objective observation, and the insomnia and tremors present in some cases are due to stimulation of the central nervous system. Leake, Loevenhart and Muehlberger attribute the headache under ephedrine to the changes in pressure in the arteries or veins within the skull. Occasionally, the untoward symptoms in some individuals disappear on repeated administration of ephedrine, showing that these individuals become better accustomed to the drug. Althausen and Schumacher mention two such cases and Hollingsworth another.

Investigators seem to agree that the prolonged use of ephedrine does not have any cumulative harmful effects and does not result in habit formation. Middleton and Chen reported a case that received a total quantity of 10 grams of ephedrine sulphate in a period of 11 days but showed no detectable pathological changes. Withdrawal did not give that patient any discomfort or any craving for the drug. Wu and Read mentioned a case in which ephedrine therapy (40 to 60 mgm. every 1 to 3 days) was continued for three years. Laboratory examinations did not show any ill effects. Thomas and Balyeat, and Collina also express the opinion that ephedrine is not a habit-forming drug. In 5 out of 51 cases of asthma and hay fever, Althausen and Schumacher noted a considerable diminution of action in the relief of attacks, showing the increase in tolerance by repeated administration. It should also be borne in mind that the attacks may not have been of equal severity and that severe cases are unfavorable for the action of ephedrine.

Contraindications are but few. In all cardiac disorders, especially with signs of decompensation, ephedrine should be used with caution. Ségard mentioned angina and hypertension as contraindications of the use of ephedrine. However, recent work on spinal anesthesia shows that it is permissible to use ephedrine in hypertension cases. Care should also be taken in cases where there is a labile vagosympathetic equilibrium, although there is not the same extent of hypersensitiveness to ephedrine as to epinephrine in Graves' disease (Csépai and Fernbach). In late acute circulatory collapse, it is best not to give ephedrine, since it may be a dangerous procedure, as shown by Blalock in experimental animals.

Pitkin mentions two fatalities in spinal anesthesia which were attributed to 50 mgm. of ephedrine, but his own toxicological studies do not seem to support this statement. Sise knows of two similar cases, not of his own; each patient was in very poor general condition, received repeated doses of ephedrine, totaling about 150 mgm., became cyanotic, fibrillated and, although the pressure was at or above normal, died in about 12 hours. In experimental animals, however, death never occurs if the blood pressure is at its normal level.

V. THERAPEUTIC USES

1. In asthma

Following the publication of T. G. Miller, who first employed ephedrine in the treatment of bronchial asthma, many other investigators have made similar reports concerning their experience with the drug. It appears to be generally agreed now that ephedrine is a good palliative remedy in the treatment of bronchial asthma. Its action is weaker than that of epinephrine, and it is therefore only occasionally efficacious in severe attacks of asthma. In mild and moderate cases it may prevent the attack if it is given several hours beforehand, abort the attack if it is administered during the prodromal period and sometimes stop the attack when it is used while the attack is in progress. Its prophylactic action seems to be better than its antispasmodic property. This is well illustrated by the work of Vallery-Radot and Blamoutier, who showed that ephedrine was effective in 16 (69 per cent) out of 23 cases when given prophylactically but in only 17 (43 per cent) out of 39 cases when given during the attack. Leopold and Miller show that the best results are obtained in allergic and reflex nasal cases, and comparatively less satisfactory results are obtained in the infectious type. Similarly, Gay and Herman note that the relief from an asthmatic attack is most quickly obtained in patients whose symptoms are due to a specific foreign protein, such as pollens, animal emanations, orris root, feathers, with or without secondary bronchitis. According to Thomas, a field for the use of ephedrine appears to lie in its employment as often as necessary to prevent the occurrence of paroxysms in asthmatic patients who are awaiting the completion of skin tests, courses of vaccine administration, rhinological treatment, radiotherapy or other methods from which more permanent benefit is hoped for. This author adds, however, that patients who are about to undergo sensitization tests should be cautioned not to seek relief in ephedrine within a period of 12 hours before such tests are to be made, for the drug, like epinephrine, temporarily prevents the appearance of positive reactions to specific tests for sensitiveness.

When desirable effects occur, ephedrine has certain advantages over epinephrine from the therapeutical point of view. In the first place, it can be given by mouth; secondly, it can be employed as a preventive; thirdly, it has a more prolonged action, although its onset is not so prompt; and fourthly, it produces less side reactions. Some individuals who are unable to take epinephrine are fortunately able to use ephedrine without untoward symptoms. In other words, a reaction from epinephrine does not indicate that ephedrine likewise will have a

TABLE 3

Results of ephedrine therapy in the treatment of asthma

AUTHOR	NUMBER OF CASES	RESULTS
T. G. Miller (1925)	7	Benefit in 6; none in 1
T G. Miller (1926)	36	Good results in 26; relief not marked in 4; no improvement in 6
Leopold and T. G. Miller (1927)	59	Complete relief in 33; partial relief in 17; no relief in 9
Thomas (1926)	20	Relief in 17
Thomas (1927)	Over 300	Ephedrine is a remarkably efficient drug
MacDermott	20	Relief in most cases
Pollak and Robitschek	16	Ephedrine replaces epinephrine injections
Hess	15	Very good in part; good in part; rarely insufficient success
Heller	1	Marked improvement (observation made on himself)
Jansen	?	Favorable
Kämmerer and Dorrer	9	Relief in 8; none in 1
Middleton and Chen	25	Relief in 9; improvement in 8; inconclusive in 8
Piness and Miller	110	24 severe cases did not obtain relief
Althausen and Schumacher	39	Complete relief in 21; partial relief in 15
Wilmer	100	Relief in 75; relief in severe attacks, 10
Wilkinson	12	Excellent
Wu and Read	(Ward) 11	9 responded well
	(Ambulatory) 90	Favorable
Bibb	2	Perfect relief
Balyeat	Over 100	Ephedrine is of considerable value in 65 per cent of the cases
Rudolf and Graham	(Severe) 2	Ephedrine reduced epinephrine injections in one, but had no effect in the other
Jankowski	11	Ephedrine has a marked effect
Collina	14	Complete relief in 5; evident improvement in 5; temporary improvement in 2; no change in 3
Taylor	10	Prompt relief in every case

TABLE 3—*Concluded*

AUTHOR	NUMBER OF CASES	RESULTS
Gay and Herman	100	Complete relief in 71; moderate relief in 21; no relief in 8
Vallery-Radot and Blamoutier	49	In 23, ephedrine used prophylactically, produced benefit in 16 but none in 7; in 39 ephedrine given during the attack, gave relief to 17, but none to 22
McPhedran	12	Complete relief in 9; partial in 2
Ségard	?	Total relief in mild cases
Long	?	Effective in relief and prevention
Munns and Aldrich	(Children) 22	Complete relief in 12; partial in 4; none in 6
Anderson and Homan	(Children) 5	Marked relief
Stewart	29	Relief in over half

similar unpleasant effect. A combination of epinephrine and ephedrine has been found efficacious by some and objectionable by others. On the whole, if the patient shows reactions to epinephrine alone, or to both epinephrine and ephedrine, the injection of epinephrine in the presence of ephedrine usually exaggerates the untoward symptoms (Althausen and Schumacher, and Haintz). If the patient can tolerate both drugs well, there is no reason why epinephrine cannot be given in addition to ephedrine if the latter fails to act.

Relief from ephedrine takes place in 20 to 30 minutes if it is given by mouth but in 10 to 15 minutes if it is administered intramuscularly or subcutaneously. The clinical improvement can sometimes be observed objectively. It consists in diminution of cyanosis, increase of vital capacity, decrease of râles, gradual disappearance of orthopnea, and euphoria of the patient. Subjectively, the patient usually volunteers the information that he can breathe better and feels relieved. The relief may be followed by coughing and expectoration (Heller). Individuals who suffer regularly from daily or nightly paroxysms may remain asthma-free for long periods of time by taking the drug once, twice or three times every 24 hours. They can resume their daily activities and pass comfortable nights. Withdrawal of the ephedrine results in recurrence of asthmatic symptoms. Other persons are not so fortunate, for the by-effects, occasionally met with, render its use impracticable even though it relieves the bronchospasm.

In children afflicted with asthma the same beneficial results have been obtained with the proper doses of ephedrine, as reported by Munns and Aldrich and by Anderson and Homan.

The results of various workers, not only in this country but in various parts of the world, are summarized in table 3. It will be seen that beneficial results have been obtained in the majority of cases by each physician. It is futile to compare the percentage of improvement in different series since the essential factor is not the patient or the drug but the severity of the asthmatic attack.

2. In hay fever

Gaarde and Maytum in 1926 reported their first series of 26 cases of autumnal hay fever which were treated by the oral administration of ephedrine. Thirteen of these patients obtained complete or almost complete relief from symptoms by taking 60 mgm. doses 2 to 3 times every 24 hours. The relief lasts 3 to 7 hours after each dose. Excessive nasal secretions stop, ocular symptoms disappear, and in every way the patients are entirely comfortable. In 5 cases the result was fair and partial relief was obtained for 2 to 3 hours after each dose. In 8 cases the results were negative. In their next series, published in 1927, they made a comparison of the effects of oral administration with those of a 3 per cent nasal spray. In 24 patients who received ephedrine by mouth, 13 (54 per cent) were completely or almost completely relieved for 4 hours or more; 7 (29 per cent) were partially relieved; and 4 (16 per cent) were not relieved or they were not able to tolerate the nervous symptoms. In a similar series of 25 cases which were given ephedrine by a spray, 7 (28 per cent) were markedly relieved for several hours; 12 (48 per cent) were partially relieved for several hours or completely relieved for less than an hour; and 6 (24 per cent) were not benefited. Ephedrine given in 3 per cent solution as a nasal spray, therefore, appears to be less efficacious and the relief is of shorter duration. However, the majority of patients feel that its use adds to their comfort. The best results are obtained when the spray is used early in the paroxysm. The effect of both the local and internal administration seems to depend on the severity of the paroxysms and the good results are obtained in the milder seizures. Untoward symptoms, when they occur, are attributable to the neurotic temperament and nervous state of the patient. In analyzing their data of two successive seasons, Gaarde and Maytum conclude that ephedrine should be given a definite place in the treatment of autumnal hay fever, and they emphasize the fact that when good effects are obtained they are temporary and symptomatic. Leopold and Miller observed complete temporary relief in 63 per cent of 11 cases and prefer the oral route for the administration of ephedrine. Encouraging results in the treatment of hay fever with the new drug are also noted by Thomas, Balyeat, Althausen and Schumacher, Wilkinson, and Ramirez. Piness and Miller observed relief in only 1 out of 5 cases when ephedrine was given by mouth, but in 18 out of 20 cases when the drug was used as a spray. These results show that local application is more efficacious than oral administration.

3. In bronchitis and emphysema

In 11 cases of senile emphysema, 1 with active and 6 with inactive pulmonary tuberculosis and all having hypotension, Saxl reports that ephedrine produced a striking improvement of the dyspnea in 8 but had no effect in 3. The blood pressure rose 15 to 30 mm. Hg for several hours with 100 mgm. doses. According to him ephedrine has the advantage over atropine in that it does not cause dryness of the throat. These conclusions have been confirmed by the study of a larger series of cases by himself.

4. In whooping cough

Anderson and Homan were the first to try out ephedrine therapy in pertussis. They noticed that the drug abolished the characteristic signs of whooping cough in 18 out of 20 children. In all instances in which improvement occurred, some cough remains but in mild form and of a type associated with acute upper respiratory infections. They believe that ephedrine is most useful during the second stage of the disease. In a series of 35 children suffering from pertussis Stewart observed that ephedrine relieves the coughing, the whooping and vomiting in mild and moderate cases. In severe cases there is no effect at all. He states, however, that the drug, combined with belladonna and ipecac, seems to have a beneficial effect. The progress of the infection is not in any way influenced.

5. In spinal anesthesia

The blood pressure-raising property of ephedrine appears to be most useful in spinal anesthesia. Rudolf and Graham studied 26 cases under spinal anesthesia, in the surgical and gynecological wards of a hospital, in which they administered ephedrine intravenously. Their results are striking, especially with reference to the elevation of the blood pressure. In their first few cases the blood pressure was allowed to drop until it had apparently reached its lowest level and then 50 to 100 mgm. of the drug were given by vein. With but one exception there quickly resulted an extraordinary and prolonged rise in blood pressure, with a slower and stronger heart beat. This lasted for 1 to 1½ hours. In their later cases they used smaller doses and gave the ephedrine within 2 to 3 minutes after the anesthetic, so as to anticipate the fall rather than combat it after it had developed. This improved technique proved to be satisfactory and they had no case of drastic fall in blood pressure or of vomiting, which occurs frequently in spinal anesthesia. They also state that the drug can sometimes be given with advantage before the spinal anesthetic where the blood pressure is already too low. Ockerblad and Dillon have used ephedrine in 50 to 100 mgm. dosage, subcutaneously or orally, in a series of 250 cases and have been successful in restoring the right amount of arterial tension necessary for surgical operations and the well being of the patient. The fall in pressure must be anticipated if the best results are to be obtained with ephedrine. In other words, once the pressure falls as much as 50 per cent, the return to the normal level—even under comparatively large doses of the drug—is slow and uncertain. It is better to reinforce the vascular system with ephedrine before the actual administration of the spinal anesthetic, to have the blood pressure 20, 30 or more millimeters Hg above the normal for that individual. The drug is repeated if there is a tendency to fall. Chronic hypotension, which used to be a contraindication to spinal anesthesia, is no longer a valid objection. Ephedrine relieves any tendency toward retching and vomiting which, according to Ockerblad and Dillon, is due to the preliminary hypodermic injection of morphine and scopolamine. Pitkin uses 1 to 1.3 cc. of a solution containing 1 per cent of novocaine and 3 per cent of ephedrine to make a wheal at the site of, and before, lumbar puncture. He is satisfied with the pressor action of ephedrine and performs operations below the diaphragm. He states that the action of the drug can be relied on for 2 to 3 hours and has contributed much to the safety of spinal anesthesia. Pitkin and McCormack, and Cosgrove have tried the drug in obstetrics where spinal anesthesia may be indicated, as in low forceps extraction, episiotomy, perineorrhaphy, dilatation or incision of the cervix, podalic version, craniotomy and extraction, vaginal hysterectomy, etc. Ephedrine is used prophylactically as outlined by Pitkin. Holder gives ephedrine subcutaneously 15 minutes before the administration of the spinal anesthetic and succeeds in keeping the systolic blood pressure at a constant level, although somewhat below the original. In 151 cases, approximately one-half received ephedrine (50 to 100 mgm.) and the average drop of blood pressure was 12.8 mm. Hg. In the other half the average drop of pressure was 37.5 mm. Hg. Wehrheim reports his experience in over 300 cases of spinal anesthesia with ephedrine (50 mgm.) injected subcutaneously 5 minutes before the spinal tap. To show the benefit of this procedure, he states that the average drop in blood pressure in spinal anesthesia without ephedrine is 10 to 30 mm. Hg within 15 minutes, but the average drop in 30 consecutive medicated cases was nil. Sise considers the repeated injection of ephedrine unnecessary and sometimes dangerous if the blood pressure begins to drop in spite of the use of ephedrine. Other measures, such as saline infusions with small doses of epinephrine, should be resorted to. Other favorable reports of spinal anesthesia with ephedrine have been made by Babcock, Wallace, Jeck in kidney and ureter operations, DeCourcy, Case who uses the drug subcutaneously immediately after the spinal injection, Gosse, Saklad, and Russell who injects ephedrine intramuscularly before the spinal puncture.

6. In hypotension

The use of ephedrine in the treatment of chronic or subacute hypotension has, with some exceptions, not proved as promising as had been hoped for. It has been tried in Addison's disease. Chen and Schmidt mentioned a single case in which ephedrine seemed to have a good effect. T. G. Miller studied two cases of early Addison's disease and found a rise of blood pressure and increase of basal metabolic rate following the administration of ephedrine, but both patients died from the disease. Rowntree and Brown treated 14 cases of Addison's disease and two of questionable Addison's disease with ephedrine. They also demonstrated a definite rise of blood pressure and increase of metabolic rate, but the rise was not accompanied by a marked feeling of well being, significant increase in strength or relief from the gastric symptoms or circulatory asthenia. Only in one case of early Addison's disease excellent clinical results were obtained. The feeling of weakness and exhaustion disappeared and the patient felt buoyant, strong and refreshed.

T. G. Miller tried ephedrine in a number of cases with essential or chronic hypotension and observed that in some of them it produced a temporary elevation of pressure, lasting from 3 to 6 hours after each dose by mouth. The response in pressure increase was not as striking as in certain other types of cases, and sometimes a dose of 50 mgm. had no effect whatever on the hypotension, yet most of the patients expressed themselves as feeling stronger and more energetic under its influence. Rowntree and Brown administered ephedrine in 9 cases of nervous exhaustion and hypotension. Aside from the rise of blood pressure for 3–6 hours and some increase of the basal metabolic rate, no other evidence of clinical improvement was observed objectively, although some of the patients were convinced that they felt somewhat stronger. Pollak and Robitschek mentioned a case of pneumonia in which daily doses of ephedrine raised the blood pressure from a level below 100 mm. to 145 mm. Hg, although accompanied by some untoward symptoms. Hess reported a series of cases with hypotension, including pneumonia, bronchopneumonia, pulmonary tuberculosis, cardiac insufficiency and vasomotor weakness. Repeated small doses of ephedrine produced favorable results. In the treatment of paresis with malarial fever, the drug can maintain the blood pressure at the normal level, as shown by three cases. He advocates the combination of ephedrine with atropine in the treatment of bronchial asthma and with digitalis or caffeine in cardiac insufficiency with low pressure and chronic bronchitis. Middleton and Chen studied three patients who had hypotension—two with asthma and one without asthma—with ephedrine at frequent intervals for a considerable length of time, in the hope of elevating their blood pressure and maintaining the higher pressure. The results in two were practically negative. The slight elevation in the third was probably due to the improvement of his asthmatic condition under ephedrine therapy. Wu and Read, on the other hand, state that they obtain very satisfactory results with ephedrine in cases of hypotension. Althausen and Shumacher determined the value of ephedrine in 7 patients with chronic hypotension. During an average period of 20 days the blood pressure was raised by daily doses of the drug and three patients felt stronger while four did not notice any change. Ghrist and Brown reported an interesting case of postural hypotension with syncope, in which ephedrine raised and sustained the blood pressure and rendered the patient free from symptoms. He has been able to go back to work without further attacks by the daily use of the drug. These authors believe that ephedrine may exercise a specific alleviative effect on the disease.

7. *In shock*

In acute circulatory collapse it is still a question how much good ephedrine can do. The drug is not indicated in late stages of shock. Chen in dogs observed that ephedrine restores the blood pressure in hemorrhage and in experimental shock induced by histamine, peptone, anaphylaxis or surgical manipulation, and that it fails to act when the heart beat becomes impaired or respiration ceases, or the degree of shock is too extensive, or when the hemorrhage exceeds 25 per cent of the total blood volume. Blalock, also experimenting with dogs, concluded that in less severe cases of shock ephedrine works better than caffeine, strychnine, epinephrine and digitalis, but in severe cases it seems to hasten death. Chen and Schmidt investigated its effect in surgical shock in a single patient, with encouraging results. Miller reported real improvement in two cases in profound shock. In one of them an intravenous injection of 100 mgm. raised the blood pressure from practically zero to 65 mm. Hg, although the patient finally died of general peritonitis. Since then, he has tried the drug in a large number of cases of shock and hemorrhage, usually without beneficial result, even though the drug was given intravenously (unpublished).

Pollak and Robitschek recorded a case of acute alcoholic poisoning in which ephedrine caused a definite increase in blood pressure from an almost imperceptible pulse. Similarly, in a patient dying of post-operative peritonitis Rudolf and Graham administered 100 mgm. of ephedrine intravenously. The systolic blood pressure rose from an unrecordable level to 86 mm. Hg. within 2 minutes and later to 130 mm. Hg. The good effects lasted for some 45 minutes and then the patient gradually sank and died some five hours later. Althausen and Schumacher reported two cases in a state of surgical shock in which ephedrine was given. One of them rapidly recovered and the other died. Both were given blood transfusions simultaneously. Waters (cited by Jackson) believes that the chances for a favorable result from the action of ephedrine are much increased if it is given in the early stages of traumatic or surgical shock. H. Schmidt advocates the use of ephedrine as a prophylactic measure against vascular shock in local anesthesia and surgical shock in major operations under chloroform, spinal or avertin anesthesia. The action usually lasts longer than the operation.

8. In Adams-Stokes' syndrome

In a single case of complete heart block T. G. Miller gave a subcutaneous injection of 100 mgm. of ephedrine: it caused an increase of the ventricular rate from 38 to 55 per minute, of the auricular rate from 110 to 125 per minute, accompanied by a rise of blood pressure, as shown by electrocardiograms. The shape of the P-wave and the ventricular complexes was observed to alter from time to time. Hollingsworth was the first to report a case of Adams-Stokes' syndrome in which the first dose of ephedrine (50 mgm.) by mouth stopped the attacks within 30 minutes. The latter did not recur in 36 hours. On taking the drug every morning the patient was completely freed from symptoms and was able to resume her household duties. After three weeks the drug was withheld but the attacks recurred in 48 hours. It was therefore resumed. Stecher reported a similar case of complete heart block with syncope and convulsions in which ephedrine gave complete relief. The patient was given 30 mgm. doses three times a day during the first week and 20 mgm. doses three times a day during the next two weeks. The drug was then discontinued and the patient had no further attacks for 10 weeks afterwards, during which time he was ambulatory.

9. As a nasal astringent

Dr. Alice H. Cook (cited by Fetterolf and Sponsler) was the first to use ephedrine locally in the nose and throat. She found that a 10 per cent solution of ephedrine causes almost instant shrinkage of an engorged nasal mucous membrane and that the action is more rapid and complete than that of a 4 per cent solution of cocaine. This subject was investigated more thoroughly by Fetterolf and Sponsler who used a 5 per cent solution in 17 patients and found it so effective that they described ephedrine as a drug which, for use in the nose, has all the advantages of epinephrine with perhaps none of its disadvantages. Following the application to the anterior part of the lower turbinate by means of a cotton brush, contraction begins in from a few seconds to one minute. The maximum is established in from 1¼ to 5 minutes or in an average time, for their series, of 2⅓ minutes. In spite of a small area of application the turbinate in every case contracts throughout its entire length. The general outline of the medial surface changes from convex to concave. Contraction is so complete and the mucosa becomes so thin and flat that it fits the bone as a glove fits the finger. The color is altered to a paler hue and assumes a gray tint at the maximum of the action. No white ischemia occurs, as is often seen with epinephrine. Relaxation begins in 2 hours and 35 minutes and is complete in an average time of 3 hours and 17 minutes. There is no sign of irritation of the mucous membrane, such as sneezing, either on the same day or the following day. There is no secondary congestion, as with epinephrine. Similar favorable results have been obtained with weaker solutions (1 to 3 per cent) by Fiske, Proetz, and others. Kennon advocates the use of ephedrine in (1) acute nasal accessory sinus disease, (2) chronic nasal sinus disease where surgery is contraindicated and as an adjunct to surgery, and (3) chronic accessory sinus disease in children where surgery should be used only for the removal of toxic foci. Merkel states that a 3 per cent solution of ephedrine is just as effective as a 5 per cent solution in rhinotherapy and the drug can be applied by (1) spraying, which is best for children, (2) topical application with cotton on a probe, and (3) introduction into the nose on cotton packs. Fifteen infants having definite evidence of ethmoiditis were treated by this author in the following manner: the nose was irrigated with a warm saline solution twice daily; half an hour after the irrigation a 2 per cent solution of ephedrine was sprayed on the nasal mucosa; and 5 minutes later 3 drops of a 5 per cent solution of argyrol were placed in the nostril. Twelve patients at least were benefited by such a régime. Ephedrine does not need to be in contact with the nasal mucosa for more than a few seconds. A pack left in situ for 3 minutes causes no more contraction than after a shorter time. Daily use over a period of 10 days shows no change in the rapidity or duration of the action. The drug brings about free ventilation and drainage for a period of 3 to 6 hours. Merkel also tried ephedrine in 3 cases of epistaxis and claimed to obtain good results. Reaves, employing a mixture of 1 per cent of ephedrine and 0.5 per cent of butyn, performs minor surgical operations on the nose. Gaarde and Maytum reported that ephedrine given orally produces a stoppage of excessive nasal secretions in cases of hay fever. They noticed sneezing in some patients. Leopold and Miller observed actual shrinkage of the nasal mucous membranes in similar cases by the same method of administration. In experimental animals (dogs), a contraction of the nasal mucosa and accessory sinuses following the intravenous injection or local application of ephedrine has been demonstrated by Rudolf and Graham with Copeland's technique, by Jackson with his own device and by King and Pak with Tschalussow's nasal plethysmograph.

10. As a mydriatic

The first ophthalmological work with ephedrine was done by Miura in 1887. He observed that a 6 to 7 per cent solution of ephedrine produces mydriasis in most people in from 40 to 60 minutes. The use of a 10 per cent solution in 18 patients did not cause a maximal dilatation of the pupil but produced sufficient dilatation for the visualization of the retina. During dilatation the light reflex is retained and the accommodation is not paralyzed. There is no increase in intra-ocular pressure, no irritation or inflammation follows its instillation and no ill effects result from prolonged use. One patient receiving three treatments daily for 15 days showed no pathological changes. The duration of mydriasis varies from 5 to 20 hours. Children and aged people are more susceptible than young adults. The diseased iris does not seem to respond well. De Vriesse published practically identical results in 1889. Inouje encountered a case in which the instillation of ephedrine precipitated an acute attack of glaucoma. Groenouw reported 100 cases he studied in which the following mixture was used: ephedrine hydrochloride, 1 gram; homatropine hydrochloride, 0.01 gram; and water, 10 cc. Merck named this mixture *Mydrin.* The mydriasis with this combination begins in 8½ minutes, reaches its maximum in 34 minutes and lasts for from 4 to 6 hours. The accommodation is not interfered with by this solution. In strong light the pupil contracts to 5.6 mm. in diameter. Similar favorable results have been reported by Suker, Snell, Cattaneo and Stephenson. Marmoiton not long ago (1911) gave a résumé of this work on ephedrine. All these authors advocated the use of ephedrine in the exploration of the fundus on account of the rapid action, absence of cycloplegia, short duration of mydriasis and harmlessness of the drug. Since the recent extensive study of ephedrine interest in its use in ophthalmology has been revived. Middleton and Chen observed that a 10 per cent solution of ephedrine, or the same concentration with the addition of 0.1 per cent of homatropine or of 0.1 per cent of atropine, may be used locally as a mydriatic for routine ophthalmoscopic examinations. Chen and Poth found that ephedrine is an efficient mydriatic for Caucasians but is of little value in dilating the pupil of the Chinese and of negroes. The investigation was made both in diffuse daylight and under controlled illumination with accurate measurements. The same difference in mydriatic action in these three races was observed with cocaine and euphthalmine, which have hitherto been used indiscriminately in clinics. The question seems not to be entirely one of different amounts of pigmentation, as rabbits of various colors respond almost equally to ephedrine applied to the conjunctival sac. Howard and Lee also reported that ephedrine is more effective as a mydriatic in individuals with light irides than in those with dark. Dittmann, on applying a 3 per cent solution on himself, experienced conjunctivitis, increased tension and blurring of vision. Schoenberg, on the other hand, concluded, from a study of several hundred patients, that a 1 to 3 per cent solution of ephedrine is a valuable drug to produce mydriasis for ophthalmoscopic examination. The same author observed that the effect of ephedrine on the human pupil is counteracted by pilocarpine within 5 to 10 minutes. Similarly, Müller, after 2½ years' experience, considers it as a useful agent for diagnostic purposes. This investigator administered ephedrine in several cases of chronic glaucoma and found no change in the intra-ocular pressure. Recently, Chen and Poth found that the dilated pupil in Caucasians under the influence of ephedrine is made more stable to light if a small amount of homatropine or euphthalmine is added. The mixtures have a short duration of action and some (but only little) influence upon the accommodation. As a result a better view of the eye ground is obtained without inconveniencing the patient by blurring of vision. The solutions are but little irritating. Some subjects experience a burning sensation which lasts for about 30 to 60 seconds. In uveitis and iritis, however, ephedrine, or its mixtures with other mydriatics, fails to dilate the pupil.

11. As an antidote for narcotic drugs

C. F. Schmidt observed in experimental animals that ephedrine possesses the power not only to increase the O_2 supply of the brain by its pressor action but also to stimulate the respiratory center directly. He advocates the use of ephedrine and epinephrine in serious depression or failure of the respiration, such as following morphine, in preference to the conventional respiratory stimulants, as caffeine, atropine, strychnine or camphor. Similarly, Kreitmair found that in rabbits and cats ephedrine, given intramuscularly or intravenously, not only restores the respiration after its paralysis by scopolamine but also raises the blood pressure. He suggests its clinical use in twilight sleep with scopolamine and morphine, or scopolamine and eucodal (dihydroxycodeine hydrochloride). Subsequent reports seem to bear out his point. In psychiatry Guttmann used hypodermically ampules containing 1 mgm. of scopolamine and 25 mgm. of ephedrine in all cases of senile dementia, arteriosclerosis and 2 excited cardiac psychoses. During sleep these individuals had a quiet smooth breathing instead of snoring. The addition of ephedrine apparently does not affect the narcotic action of scopolamine. In surgery, Streissler reported 26 cases in which he injected subcutaneously morphine and ampules containing 1 part of scopolamine and 25 parts of ephedrine to produce analgesia and anesthesia. These drugs are given in divided dosage. According to Streissler, 2½ hours before the operation the patient should be given 10 mgm. of morphine and 1 mgm. of scopolamine with 25 mgm. of ephedrine. After 15 minutes 10 mgm. of morphine are given and 15 minutes later 1 mgm. of scopolamine with 25 mgm. of ephedrine is again injected. If sleep is not deep 1½ hours before operation, 0.5 to 1 mgm. with ephedrine, which is an extra dose, should be given. Finally, ½ hour before operation, 10 mgm. of morphine, together with 1 mgm. of scopolamine plus ephedrine are injected. With these medications the pain sensation disappears before tactile sensation. There is no anxiety, fear or resistance on the part of the patient during induction of anesthesia. Many operations can be done under this form of analgesia and anesthesia, such as amputations of the breast, surgical treatment of the stomach or gall bladder, etc. In young vigorous persons ether may be given during the operation, but only as little as possible. The pulse rate is often unchanged but is usually accelerated after the operation. Respiration is slowed but not made stertorous. The blood pressure remains elevated for two hours after the operation. The patient wakes up in 4 to 6 hours with complete amnesia and euphoria and without any struggling. Vomiting does not occur. The pain in the wound is not so severe. There were no postoperative complications that could be definitely attributed to the drugs. Lubitz, working at the same clinic, reported 14 more cases, using the same medication. Moro used this combination of scopolamine, ephedrine and morphine in 32 urological cases, and Ostrčil for painless delivery. Similar results with the combination of eucodal, scopolamine and ephedrine in surgical operations have been reported by Dax and Weigand from 145 cases and by Wagner from several hundred cases. Merck has patented the scopolamine-ephedrine combination in England and Austria.

12. In dermatology

a. In urticaria. In view of the fact that ephedrine resembles epinephrine it has been tried out clinically in allergic conditions other than asthma and hay fever. T. G. Miller treated two cases of acute urticaria with ephedrine given by mouth and recorded beneficial results. Kesten made a careful study with ephedrine in a large series. She found that in 11 cases of chronic urticaria with angioneurotic œdema, 7 were cured, 2 improved and 2 unaffected. Several patients in this group had had urticaria almost continuously for years but became free from symptoms after taking the drug and remained so for some months after the medication had been discontinued. Results are less favorable in cases without œdema. Of 6 patients with chronic urticaria 2 had complete relief, 2 showed improvement and the remaining 2 no change, following the oral use of ephedrine. In 3 cases of papular urticaria, 2 of erythema multiforme and 2 of chronic eczema there was practically no relief except for lessened itching. Similarly, in a case of mild urticaria following the administration of serum but with no other symptoms of serum sickness, ephedrine produced no relief. Althausen and Schumacher reported that ephedrine gave prompt relief from itching and brought about disappearance of the lesions in a case of toxic erythema accompanied by pruritus, and effected improvement in 2 cases of urticaria but gave no relief in 5 other cases of urticaria and 3 cases of angioneurotic œdema. Encouraging results were obtained by Thomas in a few cases, and by Munns and Aldrich in a case of urticaria; by Berger and Ebster in a case and by Wilkinson in 2 cases of chronic urticaria; by McPhedran in a case of angioneurotic œdema; and by Ségard in a case of painful and purulent polymorphous erythema.

b. In dermatitis medicamentosa. Perutz recommends the use of ephedrine in anaphylactic reactions from turpentine. Stokes and McIntyre studied 68 cases which showed reactions towards arsphenamine injections. They found that in 57.5 per cent of them ephedrine relieved such symptoms as nausea, headache, vertigo, dizziness, urticaria, pruritus, pain, choking, coughing and repeated nitritoid crises. Besides, ephedrine reduced the fall of blood pressure from 28 to 6 mm. Hg.

c. In leprosy. The fact that epinephrine relieves the nerve pains of lepers led Muir and Chatterji to use ephedrine for this purpose in 13 cases. They found that ephedrine does not interfere with the simultaneous use of potassium iodide, and its action lasts for 12 to 24 hours. In their opinion, the beneficial effect is probably due to contraction of the arterioles of the nerve trunks, thereby relieving their vascular engorgement. They admit that in certain cases ephedrine does not give relief. Cochrane and Mittra reported 10 cases of leprosy in which the lepra reactions, such as nerve pain, joint pain, swelling and other manifestations, were controlled by ephedrine. They consider it an extremely useful drug in relieving the distressing symptoms of lepra reactions. The relief is usually complete. Ephedrine has no action on the temperature, nor does it reduce the eruptions which appear during reactions in skin cases. According to these authors, the lepra reactions are allergic manifestations and ephedrine like epinephrine, is able to alleviate allergic conditions.

13. In dysmenorrhea

Assuming that dysmenorrhea is due to local or general increase of parasympathetic activity, Lang used ephedrine in 30 cases of essential dysmenorrhea. There was not only complete freedom from or diminution of pain, but also diminution of menstrual flow by one-half to one-third. Ephedrine was given as soon as pain appeared, usually 2 to 3 times a day. One patient experienced pain and a feeling of cold in the legs. Palpitation and tremor were observed in other cases. In one patient, repeated curettage did not produce any effect, but the use of ephedrine actually yielded good results.

VI. ACTION OF SYNTHETIC EPHEDRINE AND COMPOUNDS OPTICALLY ISOMERIC WITH OR RELATED TO EPHEDRINE

1. Synthetic or dl-ephedrine

No sooner was the natural or *l*-ephedrine introduced to medical use than the synthetic or *dl*-ephedrine became a subject of study. It is optically inactive and is marketed by Merck under the name of *Ephetonin.* Kreitmair showed that qualitatively there is no difference between the action of natural and synthetic ephedrines. Thus, it has a prolonged pressor action, antispasmodic action, detoxifying action against scopolamine or morphine, oxytocic action and effectiveness by mouth. His results are in general confirmed by Chen and by Pak and Read, although the last two authors believe that the synthetic product is less sympathomimetic than the natural. Coelho in chloralosed dogs observed with electrocardiograms the appearance of extrasystoles, changes in Q.R.S. and alteration in T waves, block, and finally ventricular fibrillation, with various doses of synthetic ephedrine. As with the natural drug, Chen found relaxation of the isolated rabbit's intestine, hyperglycemia in rabbits, mydriatic action in animals and in men, contraction of the nasal mucous membrane and accessory sinuses and a decrease followed by an increase of the kidney volume, with synthetic ephedrine. He also observed that there is a diminution or loss of pressor action if it is injected intravenously after a previous dose of itself or of natural ephedrine.

In men, Hess, Petow and Wittkower, Saxl, Berger, Ebster and Heuer, and Nardelli reported a rise of systolic blood pressure by oral or rectal administration or subcutaneous injection of synthetic ephedrine. Berger, Ebster and Heuer, and Nardelli noted a primary leucopenia and secondary leucocytosis following the subcutaneous injection of synthetic ephedrine. Lublin showed that the synthetic product, when given by mouth, like the natural, produces hyperglycemia and inhibits the conversion of carbohydrates into fat. Cannavò obtained similar results. Euler and Liljestrand showed that synthetic ephedrine in men increases the O_2 consumption and the minute cardiac output. Synthetic ephedrine delays the emptying time of the stomach and decreases the gastric acidity, as reported by Takács. Fonseca and Trincao state that oral administration diminishes but subcutaneous injection increases the gastric acidity.

Quantitatively, Kreitmair in his preliminary communication concluded that there was no difference between the natural and synthetic ephedrines. Hess shared the same opinion for men by oral or rectal administration. Petow and Wittkower, Saxl, and Berger, Ebster and Heuer, on the other hand, seem to agree that synthetic ephedrine has a weaker pressor action in men. Chen in 9 subjects found that the changes in blood pressure by the oral use of synthetic ephedrine are much less uniform than by that of natural ephedrine. Compared indirectly in pithed cats against epinephrine, the average ratio, as found by Chen, of the intensity of pressor action of synthetic ephedrine to that of natural ephedrine with optimal doses is 1:1.33. Curtis, using the same method, determined the ratio to be about 1:2. Schaumann, and Launoy and Nicolle arrived at the same conclusion. Pak and Read, making direct comparisons in anesthetized dogs, gave the ratio of synthetic to natural ephedrine as 0.7:1 (or 1:1.43), which is close to the one obtained by Chen. A quantitative difference can also be shown in their mydriatic action. Under controlled illumination and with accurate measurements, Chen determined in Caucasians the average ratio of the mydriatic action of synthetic ephedrine to that of natural ephedrine to be 1:1.29. Regarding the toxicity, Kreitmair found it to be the same in mice either by intravenous injection or by oral administration. Chen recorded that synthetic and natural ephedrines, in the form of the hydrochlorides, given intravenously, both have a M.L.D. of 60 mgm. per kilogram in white rabbits. Pak and Read state that synthetic ephedrine is less toxic than natural ephedrine in frogs, rats, rabbits and dogs; the reverse is true for hamsters. King and Pak studied in anesthetized dogs the ratio of the shrinkage of the nasal mucous membrane produced by natural and synthetic ephedrines, respectively, and determined it to be 1:0.8.

Clinically, synthetic ephedrine has been tried wherever natural ephedrine is indicated. Petow and Wittkower treated 20 cases of bronchial asthma by oral use of synthetic ephedrine. Their results showed that in 12 cases the synthetic product rendered daily injections of epinephrine and asthmolysin unnecessary, in 5 it effected transient improvement without preventing severe attacks, but in the remaining three there was no response to the drug. Fischer treated 11 asthmatics with synthetic ephedrine and recorded improvement in 10. Berger and Ebster in an elaborate investigation recorded unquestionable benefit from synthetic ephedrine in 10 cases of asthma and less significant results in 2 severe cases of the same ailment. Neustadt studied 22 cases of bronchial asthma with synthetic ephedrine, and obtained good results in 16. Ségard treated 70 cases of asthma with the same drug and reported relief in 60 per cent, temporary or irregular improvement in 30 per cent, but no effect in 10 per cent. Gay and Herman (cited by Chen) used synthetic ephedrine in 16 cases of bronchial asthma, recorded relief in 7, questionable relief in 1, and no relief in 8. Favorable results in the treatment of asthma with the synthetic compound have also been reported by Jankowski, Beck, Guttmann, and Hemming. The majority of these investigators appear to agree that synthetic ephedrine is useful, like the natural product, in the prevention and arrest of mild and moderate attacks of asthma but less promising in severe cases, and that it has a weaker action but produces less untoward symptoms than natural ephedrine. The dosage of synthetic ephedrine varies according to individual tolerance, but the average dose lies between 25 and 150 mgm. per os.

Saxl treated 11 cases of emphysema with synthetic ephedrine, and reported success in 8 but no effect in 3. Similar improvement was observed by Berger and Ebster in 3 cases of chronic bronchitis with emphysema, chronic bronchitis and bronchitis associated with pulmonary tuberculosis. In hay fever Berger and Ebster, Kreitmair and Nardelli advocated the oral use and local application of synthetic ephedrine. Berger and Ebster observed relief of headaches in one case of hemicrania with angioneurotic œdema, but no effect in a case of chronic urticaria. Improvement of symptoms was reported by Fränkel in a severe case of urticaria, by Sack in 20 cases of eczema, and by Nardelli in three cases of alimentary urticaria and two cases of arsphenamine intolerance. Michalowsky was successful in relieving malaise from roentgenological treatment, Poppe in controlling the untoward symptoms of withdrawal of morphine in two addicts, and Parade and Voit in arresting the attacks in a single case of Adams-Stokes' syndrome. In practically every instance, synthetic ephedrine was given by mouth. For acute infectious rhinitis, Berger and Ebster used a 5 per cent solution of synthetic ephedrine as a spray. Slack (cited by Chen) found that in 4 cases of hypertrophied turbinates and 3 cases of acute rhinitis, a topical application of the 5 per cent solution produces a marked contraction of the turbinates. In a few other cases of swollen turbinates, where natural and synthetic ephedrine were used side by side in the same individuals, he was unable to detect any significant difference between their constricting power. Fränkel described a case of vasomotor rhinitis in an opera singer, with symptoms of sneezing, running of the eyes and dyspnea which were controlled by the oral administration of synthetic ephedrine. Sattle advocated the use of synthetic ephedrine in ophthalmology. According to him, a solution containing 5 per cent of synthetic ephedrine and 0.3 per cent of homatropine produces good dilatation of the pupil.

2. *Pseudoephedrine*

The natural pseudoephedrine is dextro-rotatory and is obtained from several species of *Ephedra*, including the ones yielding natural or *l*-

ephedrine. The mydriatic action of pseudoephedrine was first studied by De Vriesse (1889). He observed that a 10 to 12 per cent solution when applied locally to the eye of men produces, in from 30 to 35 minutes, mydriasis which lasts from 6 to 9 hours. There are no secondary effects after a single instillation, nor after its prolonged use, and no changes in intra-ocular pressure. Günsburg (1891) in an extensive study on animals and 120 patients presented evidence that the mydriasis produced by pseudoephedrine is caused by sympathetic stimulation. Grahe (1895) observed a slight rise of blood pressure in curarized cats after subcutaneous injection of the drug, and depression, block, arrhythmia and stoppage of the frog's heart at diastole, following the administration of pseudoephedrine. Fujii (1925) made a comparative investigation of pseudoephedrine with ephedrine. He reported that pseudoephedrine has a weaker pressor action in rabbits and a weaker mydriatic action on the enucleated frog's eye. It dilates the blood vessels in small doses but constricts them in large concentrations, as shown by the perfusion of the frog's legs and the rabbit's ear. Similarly, it relaxes the isolated rabbit's small intestines in small concentrations but stimulates them in strong solutions. It contracts the isolated rabbit's uterus in all concentrations. On the basis of these data, Fujii concluded that pseudoephedrine, like ephedrine, stimulates the sympathetic nerve endings but, unlike ephedrine, acts on smooth muscles directly in small doses. The same view is held by Pak and Read and by Chopra, Dikshit and Pillai. Chen made a similar comparative study, and reported that pseudoephedrine has a weaker pressor action in dogs and in men, and a weaker mydriatic action in men. Vasodilatation in frogs and toads was reported by Loo and Read. Upon perfusion of the toad's heart, pseudoephedrine in the concentration of 1:20,000 causes a decrease in rate but an increase in amplitude. Larger concentrations (1:200) produce cessation of cardiac activity, as shown by these workers. Pak and Read found that ergotoxine does not invert, but cocaine abolishes, the pressor action of pseudoephedrine. Liljestrand observed that pseudoephedrine contracts the isolated guinea pig's uterus and human uterus and that it has a stimulating action on the fundus of the rabbit's urinary bladder but no effect on the trigone.

Quantitatively, Chen, Wu and Henriksen recently compared indirectly in pithed cats the pressor action of pseudoephedrine and ephedrine, and found the average ratio of the intensity to be 1:5.17; that is, ephedrine is about 5 times as strong as pseudoephedrine. Pak and Read, by direct comparison in anesthetized dogs, concluded that ephedrine is twice as strong as pseudoephedrine. Their method is subject to criticism, as shown by Pittenger. King and Pak compared the shrinkage of the nasal mucous membrane in anesthetized dogs with ephedrine and pseudoephedrine and found the ratio to be 1:0.38. The toxicity was compared by Fujii who found that pseudoephedrine is less toxic in frogs but more toxic in mice. In white rabbits the M.L.D. of pseudoephedrine hydrochloride is 75 mgm. and that of ephedrine hydrochloride is 60 mgm. per kilogram of body weight, as shown by Chen, Wu and Henriksen. Pak and Read reported that pseudoephedrine is less toxic than ephedrine in frogs, rats, rabbits and dogs; the reverse is true in hamsters.

Clinically, Howard and Lee tried out a 10 per cent solution of pseudoephedrine in their eye clinic and concluded that it is an uncertain mydriatic and has no place in the treatment and examination of ophthalmic diseases. Since its action is much weaker than that of either natural or synthetic ephedrine, it is not used in this branch of medicine, although it has been advocated by Chopra, Dikshit and Pillai on the basis of their experimental results.

3. Other optical isomers of ephedrine

Kreitmair showed that *d*-ephedrine is weaker in pressor action than *l*-ephedrine. This has been confirmed by Chen, Schaumann, and Launoy and Nicolle. Recently, Chen, Wu and Henriksen compared the pharmacological activity of the six optical isomers of ephedrine, courteously supplied by E. Merck of Darmstadt and Merck and Co., Rahway, N. J. The results are summarized in table 4. It will be seen that the mydriatic action of *l*-ephedrine and *d*-pseudoephedrine is greater than that of *d*-ephedrine and *l*-pseudoephedrine, respectively. When indirectly compared for pressor action in pithed cats with epinephrine, *l*-ephedrine is found to be about 3 times as strong as *d*-ephedrine, and *d*-pseudoephedrine 7 times as strong as *l*-pseudoephedrine. *l*-Ephedrine, the strongest isomer, is 35 times as powerful as *l*-pseudoephedrine, the weakest isomer of the six. When given by mouth to men in the same quantity, *d*-ephedrine and *l*-pseudoephedrine do not appear to raise the systolic blood pressure while the other four isomers do. Of the two sets of isomers *d*-ephedrine and *l*-pseudoephedrine have the least toxicity.

TABLE 4

Pharmacological activity of the optical isomers of ephedrine

EPHEDRINE ISOMER	MYDRIASIS	RATIO OF PRESSOR ACTION IN ANIMALS	PRESSOR ACTION IN MEN PER OS	M.L.D. IN WHITE RABBITS
				mgm. per kgm.
l-	+++++	35.15	+	60
dl-	+++++	26.40	+	60
d-	+++	11.90	−	80
d-Pseudo-	++++	6.80	+	75
dl-Pseudo	+++	4.00	+	70
l-Pseudo	+	1.00	−	80

4. *Compounds related to ephedrine*

It has been shown that β-phenylethylamine, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot NH_2$, has a stronger pressor action than ephedrine (Chen, Alles) but is useless when given by mouth. The M.L.D. of the hydrochloride of β-phenylethylamine in white rabbits, given subcutaneously, is 300 mgm. per kilogram of body weight.

Phenylethanolamine, $C_6H_5 \cdot CHOH \cdot CH_2 \cdot NH_2$, was first synthesized by Kolshorn (Ber. deut. chem. Gesell., 1904, xxxvii, 2474), later by Rosenmund (Ber. deut. chem. Gesell., 1913, xlvi, 1034), and Mannich and Thiele (Arch. Pharm., 1915, ccliii, 181), and is covered by two German patents (D. R. P. 193, 631 and D. R. P. 244,321). The pressor action of this compound was described by Barger and Dale (Jour. Phys., 1910–11, xli, 19) and by Hirose. Alles recently found that it has a blood pressure effect in rabbits that is initially greater than and finally comparable with that of ephedrine, and a lower toxicity in guinea pigs by subcutaneous injection. The same author states that its toxicity is higher than that of ephedrine in rabbits by intravenous injection, while Chen, Wu and Henriksen reported the reverse in white rabbits. Tainter believes that the action of phenylethanolamine is on the smooth muscles directly. Miller and Piness showed that this compound does not raise the blood pressure in men when taken by mouth and is useless in the treatment of asthma, but its activity on the congested nasal mucous membrane is in every respect comparable to that of ephedrine. Their results are in general confirmed by Chen, Wu and Henriksen.

Nor-ephedrine, $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NH_2$, was obtained in a racemic form by Rabe and Hallensleben (Ber. deut. chem. Gesell., 1910, xliii, 2622), Calliess, Nagai, and Eberhard (Arch. Pharm., 1917, cclv, 140). Nagai patented his product under the name of *Mydriatine* in the United States (U. S. Pat. 1,356,877) and in Japan (Jap. Pat. 27,056). Miura found that this compound (*mydriatine*) has a strong mydriatic action in men. The pupil begins to dilate in 20 to 30 minutes and the mydriasis lasts for 24 to 36 hours. The accommodation is not impaired. Hirose first observed its pressor action in animals. Amatsu and Kubota concluded that its action is quantitatively the same as that of ephedrine. Their data show that the M.L.D of *mydriatine sulphate*, given subcutaneously, is 0.4–0.5 mgm. per gram in frogs, and 400 to 500 mgm. per kilogram in rabbits. Chen, Wu and Henriksen conclude from their study of ephedrine homologs and isomers that primary amines are more powerful than their corresponding methylated derivatives, and predicted that nor-ephedrine would be stronger than *dl*-ephedrine. This has been found to be true. The compound also raises the systolic blood pressure in men when given by mouth in 50 mgm. dosage. Its M.L.D. intravenously in albino rabbits is approximately 70 mgm. per kilogram of body weight. Kanao succeeded in resolving the racemic mixtures of nor-ephedrine into six optical isomers. According to Hirose (cited by Kanao), the order of activity of these optical isomers is as follows:

Nor-*d*-pseudoephedrine > nor-*dl*-ephedrine = nor-*l*-ephedrine
Nor-*d*-ephedrine < nor-*l*-ephedrine
Nor-*d*-pseudoephedrine > nor-*l*-pseudoephedrine < nor-*l*-ephedrine

Nor-*d*-pseudoephedrine also occurs in Ma Huang, as shown by Smith, and confirmed by Nagai and Kanao. Chen, Wu and Henriksen reported that nor-*d*-pseudoephedrine has a weaker action than *l*- or *dl*-ephedrine, but a stronger action than *d*-pseudoephedrine. It raises the systolic blood pressure in men when given by mouth.

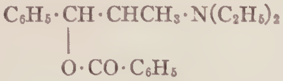
Tiffeneau, and Tiffeneau, Lévy and Boyer synthesized three compounds of the general formula $C_6H_5 \cdot CHOH \cdot CHR \cdot NH_2$, where R is ethyl, propyl or phenyl. The ethyl compound, $C_6H_5 \cdot CHOH \cdot CHC_2H_5 \cdot NH_2$, called nor-homoephedrine, has a prolonged pressor action and a M.L.D. of 130 mgm. per kilogram in guinea pigs by subcutaneous injection, and inhibits the movements of the isolated dog's intestines, as shown by Tiffeneau. Its pressor action is weaker than that of ephedrine (Chen, Wu and Henriksen). The propyl and phenyl derivatives have a depressor action, as reported by Tiffeneau, Lévy and Boyer.

Hyde, Browning and Adams synthesized a series of compounds of the general formula $C_6H_5 \cdot CHOH \cdot CHR' \cdot NHR''$, where R′ is hydrogen, methyl, or *n*-propyl, and R″ is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl or *n*-amyl. Most of these substances, including two prepared by Manske—in which R′ is methyl and R″ is oxyethyl or benzyl—were studied pharmacologically and compared with ephedrine by Chen, Wu and Henriksen. They are weaker than ephedrine. The general conclusion drawn by these workers was that with increase in the number of C-atoms in R′ and R″ the cardiac depressant action increases, the toxicity rises and the pressor action becomes a depressor action when R′ or R″ is equal to a propyl or higher alkyl group.

Kanao prepared a similar series of compounds of the general formula $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NHR$, where R is ethyl, *iso*-amyl, heptyl, benzyl, *o*-hydroxybenzyl, *o*-vanillyl, vanillyl, piperonyl, *m,p*-dihydroxybenzyl, furfuryl or citryl. He states that the hydrochloride of the citryl derivative has a strong local anesthetic action.

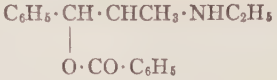
l-Methylephedrine, a tertiary amine isolated from Ma Huang by Smith, was proved to be much less active than ephedrine, a secondary amine, by Chen, Wu and Henriksen. The same conclusion was reached by Curtis with a series of tertiary amines related to ephedrine of the general formula $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NR'R''$, where R′ is methyl or ethyl, and R″ is methyl, ethyl, oxyethyl, *n*-propyl, *iso*-propyl or butyl. Some of these compounds, however, produce dilatation of the bronchi equal to that of ephedrine. The tertiary amine of the formula $C_6H_5 \cdot CHOH \cdot CHC_2H_5 \cdot N(C_4H_9)_2$, prepared by Hyde, Browning and Adams, has a depressor action, as shown by Chen, Wu and Henriksen.

Nagai synthesized the following two substances with the idea that they might possess the anesthetic property of cocaine and the styptic action of epinephrine:



$C_6H_5\cdot\underset{\displaystyle O\cdot CO\cdot C_6H_5}{\underset{|}{CH}}\cdot CHCH_3\cdot N(C_2H_5)_2$

Allocain A



$C_6H_5\cdot\underset{\displaystyle O\cdot CO\cdot C_6H_5}{\underset{|}{CH}}\cdot CHCH_3\cdot NHC_2H_5$

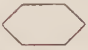
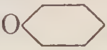
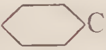
Allocain S

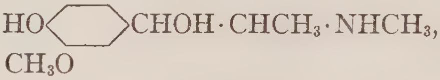
His process has been patented in Canada (Can. Pat. 177,019), Japan (Jap. Pat. 32,476) and the United States (U. S. Pat. 1,399,312). Kubota studied *allocain S* and found it to have a local anesthetic property but that it produces a primary fall of blood pressure in animals. The substance causes local irritation and necrosis so that its clinical use does not seem justifiable.

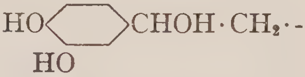
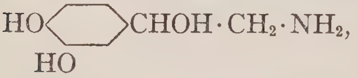
Beaufour prepared ω-methoxymethylephedrine, $C_6H_5\cdot CHOH\cdot CH(CH_2\cdot OCH_3)\cdot N(CH_3)_2$, and found it to have a local anesthetic action. Brauchli and Cloetta reported that diallylephedrine, $C_6H_5\cdot CH(OC_3H_5)\cdot CHCH_3\cdot NCH_3(C_3H_5)$, has a depressor action.

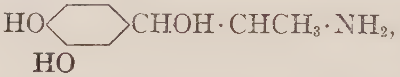
Emde and Runne synthesized α-isoephedrine, $C_6H_5\cdot CHNHCH_3\cdot CHOH\cdot CH_3$. This compound is of interest because ephedrine for some time was considered to have the same structural formula.

Dulière made synthetically several ethers of phenylpropanolamine, and studied their pharmacological action.

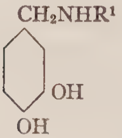
Tyramine, HO$CH_2\cdot CH_2\cdot NH_2$, was proven to have a stronger pressor action than ephedrine but to be useless when given by mouth in men, as shown by Chen and Meek. *Sympatol*, HO$CHOH\cdot CHNHCH_3$, which has recently been studied as a possible substitute for ephedrine by Ehrismann, Lasch, and Ehrismann and Maloff, has, on the other hand, a weaker pressor action than ephedrine, as observed by Chen, Wu and Henriksen. In view of the fact that the presence of an OH group at the *p*-position usually intensifies the action, and the introduction of a methyl group on the α-C-atom from the N-atom prolongs the action, Chen, Wu and Henriksen suggested the synthesis of the compound HO$CHOH\cdot CHCH_3\cdot NH_2$, which was soon achieved by Hartung of Sharp and Dohme, Baltimore. It has in fact a prolonged and stronger pressor action, and is much less toxic, than either *dl*- or *l*-ephedrine in animals, but it has not been demonstrated that it produces systemic effects when given by mouth in men. Further study is needed here.

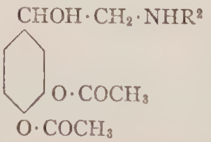
Tiffeneau, Lévy and Boyer synthesized *p*-methoxy-norhomoephedrine, $CH_3O\langle\quad\rangle CHOH\cdot CHC_2H_5\cdot NH_2$, and found it to possess a greater pressor action than nor-homoephedrine. Kohler prepared *p*-methoxyephedrine, $CH_3O\langle\quad\rangle CHOH\cdot CHCH_3\cdot NHCH_3$, and *m*-methoxy-*p*-oxyephedrine,  $\underset{CH_3O}{HO}\langle\quad\rangle CHOH\cdot CHCH_3\cdot NHCH_3$, and found them to have no pressor action in rabbits.

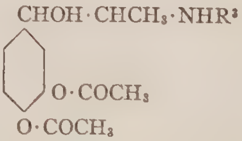
It is universally agreed that epinephrine  $\underset{HO}{HO}\langle\quad\rangle CHOH\cdot CH_2\cdot NHCH_3$, has a strong but fleeting action, while ephedrine has a weaker but more prolonged action. The latter produces systemic effects when given by mouth. *o*-Dihydroxyphenylethanolamine,  $\underset{HO}{HO}\langle\quad\rangle CHOH\cdot CH_2\cdot NH_2$, also has a stronger pressor action than ephedrine, as shown by Hirose.

The compound  $\underset{HO}{HO}\langle\quad\rangle CHOH\cdot CHCH_3\cdot NH_2$, is mentioned in the German patent literature (D.R.P. 254,438, 256,750, 269,327) and has been studied pharmacologically by Tiffeneau (1920). The latter found that an *l*-isomer resolved from its racemic mixture has 60 to 75 per cent of the activity of *l*-epinephrine, but he did not study the duration of its action nor its absorption from the gastrointestinal tract. It seems desirable to compare its action with that of ephedrine.

Kanao recently synthesized three series of compounds having the general formulae:







where R^1 is methyl, ethyl or propyl, R^2 is methyl, heptyl, benzyl, piperonyl, diacetoxybenzyl, acetovanillyl or furfuryl and R^3 is methyl, heptyl, benzyl or diacetoxybenzyl. The physiological activity of these substances has not been reported.

From the above account it appears that there is no difficulty in synthesizing compounds related to ephedrine that are stronger pharmacologically in animals, especially by making primary amines and introducing 1 or 2 OH groups on the benzene ring. A prolonged action may also be imparted to them by introducing a methyl group on the α-C-atom from the N-atom. The absorbability from the gastrointestinal tract seems to be a peculiar feature of ephedrine, and this has made ephedrine particularly useful clinically because the drug can be given by mouth. Among the synthetic compounds, *dl*-ephedrine and *dl*-norephedrine resemble natural ephedrine most closely and deserve a clinical trial. Some other compounds have a strong contracting power on the congested nasal mucous membrane in men, and a comparative study may yield profitable results.

VII. SUMMARY

The following very brief summary is made from the practical point of view.

1. Ephedrine is the chief active principle occurring in the Asiatic species of *Ephedra*. The other constituents that are present in the Chinese species are pseudoephedrine, nor-*d*-pseudoephedrine, *l*-methylephedrine, and *d*-methylpseudoephedrine.

2. Ephedrine is a stable compound. Its solutions are not decomposed on exposure to air, light or heat, or by long standing.

3. Ephedrine has been successfully synthesized by various methods.

4. In mammals, ephedrine in suitable doses raises the blood pressure, increases cardiac activity, dilates the pupil, relieves broncho-spasm, contracts the uterus, more frequently inhibits than stimulates the gastrointestinal tract. These effects can be explained by the stimulation of the myoneural junctions of the sympathetic fibers. In certain instances, there is an additional stimulation of the ganglia. It has been claimed by some investigators that it acts on the smooth muscles.

5. In animals, ephedrine does not have a marked effect on any of the body secretions.

6. There is an increase in the formed elements of the blood and hyperglycemia, following the administration of a suitable quantity of ephedrine.

7. Ephedrine increases slightly the basal metabolic rate and the oxygen consumption.

8. Ephedrine may stimulate the central nervous system.

9. Ephedrine is easily absorbed and has a low toxicity.

10. In clinical use, ephedrine can be applied locally and given by mouth or by injection. Individuals who do not have a vagosympathetic equilibrium may experience untoward symptoms.

11. Ephedrine has been used with success in the treatment of bronchial asthma, hay fever, whooping cough, bronchitis, postural hypotension and Adams-Stokes' syndrome, in combating the fall of blood pressure in spinal anesthesia, in antagonizing the action of narcotic drugs, in shrinking the congested nasal mucous membrane, and in dilating the pupil for ophthalmic examination. Its value in dermatology, shock and dysmenorrhea is promising.

12. Compared with epinephrine, ephedrine has a less intense but more prolonged action.

13. Of the many synthetic compounds, *dl*-ephedrine and *dl*-norephedrine deserve more extensive clinical trials.

This review is intended to be as concise as possible. Naturally the authors could not discuss many valuable papers as fully as they desired. The literature consists of all those articles available on or before November 1, 1929.

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THE CHOLESTEROL METABOLISM IN HEALTH AND IN ANEMIA

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HISTORY

The existence of a peculiar substance in gall stones which from its general behaviour towards solvents was regarded as being of a fatty nature was noted by Conradi (83) in 1775. The discovery of what is known as cholesterol is, however, attributed to Poulletier de la Salle, who extracted it from biliary calculi in 1758 (277) (124). Fourcroy (126) verified his data and in addition isolated an oily material from a slowly decomposing liver which from its chemical and physical behaviour he classed with spermaceti and identified with the substance previously found in biliary calculi (125). There seems to be no doubt that the material extracted by Thouret (344) in 1786 from the brains of cadavers exhumated in the *Cimetière des Innocens* and classed with spermaceti was cholesterol (127). Fourcroy called all the fatty compounds "matière adipocireuse" or adipocere, but he distinguished clearly between fat in general and cholesterol which he called "adipocire cristallisable."

At this time the theory was formulated that the spermaceti like compound existed in the animal economy and that it was separated from the brain, then deposited in the canaliculi of the liver from which it was excreted (344). Fourcroy added that it might be a product of slow decomposition (125).

Poulletier de la Salle's and Fourcroy's observations were amply verified, but much confusion existed in the literature because of the nomenclature as many authors failed to distinguish whether the adipocere was crystallizable or not. Chevreul (78) in 1814 established its true nature as a nonsaponifiable fat-like body, distinct from other forms of "adipocire" and spermaceti. He named it *cholesterine* (79) from the Greek χολή (*bile*) and σπερεός (*solid*), the name which has been used ever since. Subsequently cholesterol was reidentified in biliary calculi (71) and in many parts of the body. This early work has been admirably reviewed by Robin and Verdeil in 1853 (297).

The presence of cholesterol in the blood was indicated by Denis (91) in 1830 and definitely demonstrated by Boudet (61) (62) in 1833. Quantitative determinations of the cholesterol in the blood in health and disease were published in 1844 by Becquerel and Rodier (38).

The presence of cholesterol in various tissues and fluids was established by this early work. Very little was known about its physiology. The theory of the early investigators was accepted in the middle of the nineteenth century (68) (89) (201). Mialhe (243), however, thought that cholesterol might be formed from albuminous materials, and that because of its chemical inertia it was not destroyed in the body. It was excreted through the bile because of its insolubility in other body fluids.

Some support for the early theory about cholesterol metabolism (344) (68) (89) was given experimentally by Flint (122) in 1862, who demonstrated that the blood passing through the brain of dogs gained 23 per cent of its cholesterol and lost practically the same amount in passing through the liver. He also showed that the cholesterol excreted in the bile was changed to a substance in the intestine similar in some respects, yet totally different from cholesterol, which he called *stercorine*. He also established the absence of stercorine in the feces in obstructive jaundice and the return of this substance when the stools became normal in color.

With the discovery of a cholesterol-like body in the vegetable cell by Beneke in 1862 (40) and its differentiation by Hesse (159) in 1878, who named it phytosterin, the universal occurrence of cholesterin or its isomers both in the animal and vegetable kingdom was indicated. The progress made in the knowledge of cholesterol from the chemical, physical and biological points of view at the end of the nineteenth century was reviewed by Moore (247) in 1907.

SCOPE OF PAPER

Certain aspects of the more recent research have a distinct bearing on the cholesterol metabolism of man in health and disease. Prominent among these are the relation of cholesterol in the food to the amount in the blood, tissues and bile, the question of cholesterol synthesis and destruction, the relation of organs and cells to the metabolism of cholesterol, and its possible endocrine regulation. In addition the relation of cholesterol to blood formation and blood destruction and to anemia has been included, since the organs participating in the cholesterol metabolism, as far as is known, are intimately related to the hematopoietic organs.

The numerous methods for determining cholesterol and the normal blood cholesterol figures for man and the lower animals were recently reviewed by Weidman and Sunderman (355). The "normal" quantity in the blood varies to a certain extent with the method used and therefore in evaluating the data in the literature the standard set by each individual author has been used for comparison.

THE RELATION OF BLOOD CHOLESTEROL TO FOOD AND NUTRITION

With the discovery of cholesterol isomers in the plants (40) (159) the importance of the relation between food cholesterol and the cholesterol content of the animal organism became evident.

Many investigations have been undertaken to establish whether special types of food or withdrawal of food might influence the quantity of the cholesterol in the blood. This would furnish a simple explanation for the variations in disease especially when alimentation is disturbed. Most observers agree with Klein (180) and Mueller (249) that cholesterol is readily absorbed from the alimentary tract when suitably dissolved. Lander (197) emphasizes the ability of the rat to pick out and conserve cholesterol from a diet exceedingly low in cholesterol content.

Experimental evidence

High cholesterol or fat diet. To establish a relation of the cholesterol content in the blood to ingestion of cholesterol was attempted in 1892 by Jankau (169), in rabbits and dogs. He was unable to demonstrate an increase in the blood. Since that time various investigators have shown (248) (278) (347) (210) (36) (90) that if cholesterol, or cholesterol esters and oil are fed to rabbits there is an increase of cholesterol in the systemic circulation. The same has been found in cats (135), dogs (148) (309) (17) and goats (219). Oil alone does not produce an increase of cholesterol in rabbits (248), while foods rich in cholesterol will induce hypercholesteremia as has been demonstrated by feeding egg yolk (168), and soy bean (162). Moehlig and Ainslee (246), however, found that the cholesterol content of rabbits was not altered appreciably by ordinary feedings. Lehman (202) fed 0.3 gram of cholesterol to rabbits and obtained a decrease the first 8 hours followed by an increase averaging 20 per cent in 24 hours.

Arndt (17) found no increase of the blood cholesterol in dogs fed cholesterol, while others report a slight hypercholesteremia (11) (328). Leites (203) obtained an increase after the administration of olive oil, which Arndt (17) was unable to confirm. Foods rich in cholesterol increased the blood cholesterol in dogs slightly (98) (148) (339) (116). This increase was not usually large, however, averaging 9 mgs. per 100 cc. of blood in one series of 11 dogs (339), while Grigaut and L'Huillier (148) reported that after a progressive increase to a maximum, the blood cholesterol fell in spite of a high cholesterol diet. Bloor (52) found very small variations in cholesterol within 8 hours after food in dogs, while Knudson (185), feeding a high fat diet, could not demonstrate any increase in 24 hours. This was later verified by Hiller, Linder, Lungsgaard and van Slyke (160).

Low cholesterol diet. If food rich in cholesterol produces hypercholesteremia in rabbits and occasionally in dogs, one would expect the converse to be true. Only traces of cholesterol were found in the blood of rabbits fed for 20 days on a cholesterol free diet (98) (132), while a marked increase occurred when they were fed the same diet with the addition of cholesterol. A high carbohydrate diet caused a slight decrease of the blood cholesterol in rabbits (211) and dogs (17). Stepp (331) fed two dogs on extracted diets and found a decrease in one dog while the other showed no decrease of the cholesterol in the blood.

Clinical evidence

High cholesterol or fat diet. The reports of the influence of food on the cholesterol level in the blood of man are contradictory.

Conditions of moderate or slight hypercholesteremia have been brought about in man by feeding large amounts of food rich in fat and cholesterol (155) (208) (106) (360) (30) (294). Luden (220) demonstrated that eggs, butter and meat were especially effective, but that under ordinary circumstances the change was not very great. Orlowski (268) observed a decrease of cholesterol in the blood of 3 men after 3 days of starvation, while 3 days' feeding with bread caused an increase, which was augmented during a 3 day period of feeding with fatty foods in two, and still further augmented when to the fatty food 1 gram of cholesterol was added. One of the subjects who did not show an increase was unable to eat the fatty food. Bürger and Habs (64), and Arndt (17) feeding an oily solution of cholesterol or of cholesterol esters to normal individuals invariably found that it was followed by an increase both of the cholesterol and the fat content of the blood. Recently, McClure and Huntsinger (230) studying the influence on blood lipoids in man of single food-stuffs demonstrated that after ingestion of all kinds of food the cholesterol curve was modified. Oleic acid and olive oil caused the greatest increase, dextrose next, and eggwhite the least. With a fat free meal there was a temporary rise only. Their findings indicate that the cholesterol concentration of the blood is modified by absorption. In examining their figures it is seen that the increase is comparatively small, the maximal rise amounting to 20 mgm. per 100 cc. with oleic acid.

In contrast to this, Rouzaud and Cabanis (313) found a very slight increase in the blood of only 1 out of 11 healthy young people, four to five hours after the ingestion of a meal consisting of soup, bread, meat, peas, two eggs, and wine. Denis (92) could not demonstrate any change 3 hours after a breakfast of 4 eggs, 200 grams of mutton, 50 grams of bacon, and ½ pint of cream, bread, butter and coffee. This has been verified by Campbell (65). Blix (49) states that cholesterol is not changed after a fat meal, only the neutral fat. The same was reported by Hiller, Linder, Lundsgaard, and van Slyke (160), and Broun, Pelkan and Riggs (63) in pernicious anemia and other pathological conditions, as well as in normal individuals.

Ssokoloff (328) found no rise of the cholesterol in the blood of 2 men given 3 grams of cholesterol. In two cases of liver cirrhosis, introduction of cholesterol by mouth caused hypercholesteremia, while in normal man and various pathological conditions these amounts of cholesterol did not cause an increase in the blood. He suggests that the hypercholesteremia in liver cirrhosis may be due to injury of the liver which eliminates cholesterol. He considers that the opinion that hypercholesteremia is due to alimentary sources without influence of other factors is not tenable.

Hubbard (163) in a subject obtained the same cholesterol content of the blood before and after a period of high fat and a low fat diet. Strathmann-Herweg (334) was unable to demonstrate any difference in the blood cholesterol of infants during a six-week period on breast milk, or artificial milk with more or less fat. Chauffard, Laroche and Grigaut (75) also conclude that under normal conditions of alimentation there is no increase in cholesterol in blood after meals and that the normal equilibrium of the lipoids is not easily upset. There seems to be a tendency towards constant values for the lipoids in the blood (57) (203) (95) (62) except when excessive amounts of fat are shifted (57). It must be borne in mind, however, that considerable variations may be found between animals within the same species (203) (340) and that as a rule comparison between animals is not justifiable.

Gardner and Gainsborough (138), determining the cholesterol in normal human beings, came to the conclusion that they differ widely in total cholesterol and that these variations could scarcely be due to direct absorption of cholesterol from the food into the blood plasma. They calculated that several hours after a light meal as breakfast with an assumed cholesterol content of 0.15 gram, even if the entire amount found its way into the blood stream, this would increase the amount of cholesterol in an individual with 6 liters of blood only 0.00025 per cent, a figure well within the limits of experimental error.

Low cholesterol diet. Attempts to decrease the blood cholesterol in man by dietary procedures have been reported. Luden (220) demonstrated that on a simple diet consisting mainly of milk, bread, lettuce and jam there was a definite decrease of cholesterol in 3 days and on an exclusive meat diet a marked increase of about 100 per cent in 7 days, while on a vegetable diet it fell again. In this connection it is of interest that studies on the normal cholesterol metabolism in man in the Dutch Indies (198) show cholesterol values in the blood far below those obtained in countries where animal products constitute a great part of the diet. This is not considered as a racial characteristic but due to dietary habits. Rosenthal and Patrzek (301) in undernourishment of the war found a hypocholesteremia after a long time, while Strathmann-Herweg (334) obtained normal values in undernourished children with an exudative diathesis, and in rachitic children. No correlation could be established between nutrition and cholesterol, nor did the children fed cod liver oil show any difference.

On the other hand, Arnoldi and Collazo (18) and Luden (221) found low values in obese people. This was not confirmed by Epstein and Lande (112) reporting a single observation. Koning (188), examining people with overweight suffering from various diseases, found hypercholesteremia in all of them.

Cholesterol in undernutrition

Undernutrition as a cause for low blood cholesterol has been advocated (225) (268). Strauss and Schubardt (335) claim that inanition interferes with absorption from the intestine and that this lack of absorption may cause a lowered blood cholesterol. Rothschild and Wilensky (311), outlining the factors influencing the blood cholesterol, consider a diet poor in lipoids as one of them. Asada (23) found that in rats with shortage of food normally constituted, the fat decreased and the cholesterol increased, but that on a vitamin free diet the fat and cholesterol varied together, both being spared as long as carbohydrates were available. That food is an important factor in the maintenance of the cholesterol level of the blood was concluded by Small (324), while Rothschild and Rosenthal (310) claim that hypercholesteremia can be controlled by food. However, a decrease of the cholesteremia of nephritis was not obtained with a fat free diet (44) (276). Pribram (282) states that it is difficult to keep the blood cholesterol low with food because of the use of the tissues.

Cholesterol in starvation

The intake of food is not the only factor controlling the cholesterol content of the blood. Hürthle (166) found higher cholesterol values in starving dogs, than when they were fed horsemeat. Hypercholesteremia has also been demonstrated in starving cats (135), and rabbits (308). Arndt (17) obtained a variable result in starving dogs, and he concluded that fat dogs may have hypercholesteremia while lean dogs show hypocholesteremia. Terroine (339) and Orlowski (268) noted a decrease after starvation in most dogs. The cholesterol decreased progressively less after longer starvation, the body attempting to retain the cholesterol (268).

Arndt (17), starving for 3½ days, had hypercholesteremia. Lennox (209) found in 3 patients a steady increase in one during an 11 day fast, while the other two showed lower values during the period of starvation than before or after. Shope (321) obtained an increase of cholesterol in the blood both in animals and man during starvation.

Ellis and Gardner (105) explain the hypercholesteremia sometimes seen in starvation as due to the destruction of tissues of the animal rich in cholesterol, while Rothschild (308) considers that the cholesterol changes during starvation can be most readily explained by supposing that they are associated with the increased fat metabolism. The mobilization of fat in starvation is occasionally evidenced by an increase of the fat in the blood (319) (88) (147) (82), although several authors report very variable results (147) (227) (200) (51) (32) (133) which they explain as being due to the state of nutrition of the animal (339) (51) (32). They suggest that well supplied stores of fat lead to a hyperlipemia.

Summary

It is evident from these observations that food does influence the level of cholesterol in herbivorous animals, like the rabbit, in which a long continued feeding with cholesterol-rich food causes a hypercholesteremia, while fats apparently can not be substituted (336). In some carnivorous and omnivorous animals and in man it is possible to obtain a small temporary rise a few hours after a meal, which is missed in others. Usually an adjustment occurs, and a permanent increase does not depend upon food itself. A lowering may occasionally occur on a cholesterol poor diet but it does not fall below a certain level. Consequently one may conclude with Hueck (165) that it is probable that the body to a certain extent is independent of the amount of cholesterol in the food and that if the exogenous cholesterol fails there must be endogenous sources in the body which keep the cholesterol at a certain level.

RELATION OF BLOOD CHOLESTEROL AND BILE CHOLESTEROL

Under unusual circumstances of nutrition the level of cholesterol in the blood may be occasionally raised or lowered, but under ordinary circumstances of health the content is kept remarkably constant in the individual, which indicates that there is an efficient regulation (51), probably by the liver (133).

The excretion of cholesterol by the liver into the bile was pointed out by the early observers (344) (243) (122) and this conception is now firmly established (24) (196). The theory proposed by Nauyn (257) and his school that cholesterol is not a product of the general metabolism and not a specific excretion of the liver, but a product of the epithelium of the bilary tract and especially the gall bladder, has been refuted by Bacmeister (28) who showed that the cholesterol is present in the bile and that it is not directly or indirectly derived from the mucous membrane of the gall bladder; and by Aschoff (26)who demonstrated that the fat and cholesterol in the epithelial cells were products of reabsorption.

The mechanism of excretion is unknown, but Rosenthal and Holzer (304) suggested that the Kupffer cells take up cholesterol, and that the excretion takes place through the liver cells or perhaps in the bile capillaries. Beumer (46) considers that the liver is for the cholesterol what the kidney is for uric acid. He criticises the view of Chalatow (72) that the rôle of the liver as an excretory organ is very small, and that increased elimination through the bile is a pathological phenomenon indicating liver insufficiency, especially since Chalatow himself showed in balance experiments that the larger part if not all of the cholesterol of the food was excreted in the intestine with the bile. However, excretion through the large intestine must be considered (326).

If the liver as an excretory organ eliminates cholesterol through the bile and in this capacity keeps the level of the cholesterol in the blood constant it is evident that any flooding of the blood with this substance should be reflected in the increased cholesterol output in the bile.

Experimental data

To elucidate the relation of blood and bile cholesterol experimentally, Thomas (343) in 1890 and Jankau (169), working on dogs with experimental biliary fistulas, attempted to show a relation between food and bile cholesterol but failed to do so. Goodman (144) fed two sets of dogs repeatedly white of eggs or calves' brain and found an increase of cholesterol in the bile with both diets, although the white of eggs contained no cholesterol. Havers (153) and Fasiani (116) demonstrated that protein and fats increased the excretion of cholesterol in the bile in dogs while carbohydrates were ineffective. Stepp (331), feeding dogs with bile fistula on extracted diets, found less cholesterol in the bile while an addition of cholesterol to the food increased the cholesterol in the bile.

Arndt (16), working on dogs with gall bladder fistula with and without occlusion of ductus choledochus, and also examining bile, obtained by gall bladder puncture after laparatomy, found that alimentary lipemia was accompanied by a passing hypercholesteremia, but that the gall bladder cholesterol was not influenced in a constant manner by the cholesterol in the food. It was missed experimentally in one dog while four others showed a definite although moderate and variable increase of cholesterol in the bile. In comparison with the cholesterol fed, the increase in the bile was small. He concluded that there was a certain parallelism between blood and bile cholesterol, but that the excretion was not an immediate response, and that all the cholesterol in the food did not appear in the bile. He suggested that the discrepancy may be due to the excretion of the cholesterol through other channels, and that the conception of storage of cholesterol in the tissues was important especially in animals with bile fistula, as the tissues were deprived of cholesterol.

Beumer (47) criticises Arndt's work, pointing out that it is not permissible to take only part of the bile as indication of the total excretion of cholesterol, and he maintains that there is a very regular relation existing normally between ingested and injected cholesterol and that excreted in the liver through the bile. He demonstrated that 0.7 gram of colloidal cholesterol injected on two successive days in two infants on the same milk diet was excreted almost quantitatively. Fasiani (116) had previously shown that suspensions of cholesterol injected in the blood stream of dogs with biliary fistula increased the cholesterol in the bile. Fasiani concluded that the augmentation or diminution of the elimination in the bile is reflected in an inverse variation in the blood. That this is not always true has been demonstrated by Alpern (11) in both normal and diabetic dogs, in which hypercholesteremia was not always followed by increased excretion through the bile.

In starving dogs, on the other hand, Rothschild (308) found an increase of cholesterol both in the blood and the bile, while McMaster (232) demonstrated that the quantity excreted in the bile was decreased although the concentration was higher. This is considered by McMaster as a confirmation of Gardner's view of conservation in the body. With a diet rich in cholesterol an increase was demonstrated in the bile.

Clinical data

The correlation of blood and bile cholesterol in man offers greater experimental difficulties and the results reported are variable.

For examination, bile has been obtained from bile fistula, by the duodenal bucket and at autopsy. In cases with bile fistula in most instances a diseased condition was present. The total excretion of bile in man is a variable quantity. Hueck (165) has estimated from the data available that on an average 500 cc. is excreted, and that probably the cholesterol may vary between 50 to 250 mgm. per day.

Comparatively few investigations have been made on the relation of food and bile cholesterol in man. Bacmeister (29) observed that more cholesterol was present in the bile after proteins than after carbohydrates, while Salomon and Silva (316) found small quantities of cholesterol in the bile (duodenal bucket) when the diet was low in this substance. With increased cholesterol content in the food the elimination was augmented. Butter (315) caused a greater excretion of cholesterol than eggs although the latter contained more cholesterol.

Csyhlarz, Fuchs and Fürth (87) and Arndt (16) could not demonstrate an increase of cholesterol in the bile after a diet rich in cholesterol in patients with bile fistula. Therefore no conclusions can be drawn as to the normal cholesterol metabolism from experiments on man with gall bladder and biliary disease (16).

In a physiological condition associated with hypercholesteremia as pregnancy, Peirce (274), McNee (234), and Grigaut (149), observed a marked increase of cholesterol in the bile. Later, however, Pribram (282), investigating the bile from the duodenum in gravid women, found the bile cholesterol decreased. The same result had previously been obtained in pregnant dogs (153). The cholesterol retained in pregnancy was later found to be eliminated in the milk (157) and the bile (31). McNee's (234) results have been explained by the fact that in all his cases abortion had taken place before the determination was made (31). The results, therefore, are not uniform but the discrepancy may depend upon the time of the determination, whether late or early or after the termination of the pregnancy.

By the early workers high cholesterol values in the bile have been found in nephritis (274) (149) (76), diabetes (149) (76), and diabetes with biliary fistula (29). Later investigators (282) (34) have concluded that in hypercholesteremia from certain causes, there is a decreased excretion, consequently a retention. Grigaut (149) and Chauffard and co-workers (76) found less cholesterol in the bile in retention icterus and cirrhosis of the liver. Barat (34), in a series of cases with various clinical symptoms, found low values in endogenous hypercholesteremia as nephrosis and diabetes. The evidence obtained indicated that in all the cases with low cholesterol values in the bile in every instance insufficiency of the function of the liver could be deduced. In nephrosis an active retention and deposits in the tissues has been shown by Herrnstadt (158).

Increased blood destruction induced experimentally caused an increase of the cholesterol in the serum (193) and subsequently in the bile (193) (299) and feces (194). In human anemias with indications of increased blood destruction the tendency of the cholesterol in the serum is toward a lower level than normal. In both hemolytic jaundice and pernicious anemia examination of bile obtained from the duodenum has shown more cholesterol present than normal. This has been demonstrated by Bondi (60), Rosenthal and Holzer (304) and Barat (34). However, in two cases of hemolytic icterus with moderate jaundice and normal cholesterol values in the blood there was no increase of cholesterol in the bile (34), and normal or subnormal cholesterol values were found in secondary anemia (34). It is also of interest to note that Rosenbloom and McKelvy (300) in six cases of hemolytic jaundice that came to autopsy found gall stones in five. In one case seen by the author (253) gall stones were present in the gall bladder at the time of splenectomy. Rosenthal and Holzer (304) point out the incongruity seen in pernicious anemia and hemolytic jaundice. If the bile pigment changes are to be taken as criterion for blood destruction, in spite of the fact that hemoglobin and cholesterol become free in large amounts, the organism answers with bilirubinemia but not with hypercholesteremia. The cholesterol, however, is lost through the bile (302).

After destruction of white blood cells in leukemia by x-ray treatment an increase of the blood and the bile cholesterol could not be demonstrated (34). This result suggested that the cholesterol obtained from cell destruction may be deposited and transformed in the reticulo-endothelial system and not excreted as cholesterol (34).

Experimentally an acute lowering of cholesterol in the blood can be obtained by injection of colloids (46) (305) or oral administration of olive oil (203). The decrease in the blood was not accompanied by any increase of the cholesterol in the bile (46) (203). However, a true picture of the excretion of cholesterol may not be obtained by examination of the bile alone. Sperry (326) presented evidence to show that some cholesterol may be excreted through the large intestine, and bacterial synthesis must also be considered.

The excretion of the liver apparently is modified by splenectomy. Eppinger (110) found a decrease of cholesterol in the bile and an increase in the blood after the operation, while Goto (146) demonstrated a decrease of bile pigment elimination. The influence of the spleen on the activity of the liver has been demonstrated by Kobayashi (207), who showed a specific activating effect of splenic extract on the formation of acetone in the isolated liver, and Joannovics and Pick (208) who obtained a decreased absorption by the liver of cod liver oil after splenectomy.

The change in the liver in cholesterol retention has been claimed by Weltman and Biach (356) to be due to a "thickening of the liver filter." They pointed out the paramount importance of the liver in the cholesterol metabolism and demonstrated that in herbivorus animals like the rabbit, feeding with cholesterol caused a deposit in the organs because the liver is not suited for excretion of large amounts of cholesterol, while carnivorous animals have only a temporary cholesteremia since they are accustomed to cholesterol rich diet and eliminate the excess rapidly through the bile. Chauffard, Laroche, and Grigaut (75) also consider that the comparison of the level of cholesterol in the blood with that in the bile in different diseases will give the degree of activity of the cells which excrete cholesterol. Hueck (165), however, pointed out that if the "thickening of the liver filter" was the only determining factor one ought to have increased cholesterol in the blood in all cases of mechanical obstruction. This is not always the case as has been shown by Stepp (330) in obstructive jaundice with normal or subnormal cholesterol values in the blood which he explains on poor absorption and cachexia. Experimental ligation of the common duct caused an increase of the cholesterol in the blood (333) but did not prevent absorption of cholesterol (328) (251). Feeding high cholesterol diet under this condition caused an increase in the blood of rabbits but not in dogs (328). Thus increase of cholesterol in the blood is not always a mechanical phenomenon but may depend upon the changed colloidal state of cholesterol (115) (151) (228). Hepatectomy in dogs has given variable results. Enderlen, Thannhauser and Jenke (108) obtained no rise of cholesterol in two dogs living 7 and 9½ hours after operation, while in those living 14 and 16 hours there was a considerable rise. Mann (226), Rosenthal, Licht and Melchior (306) made similar investigations on serum after liver extirpation and did not find any increase of cholesterol in the blood.

In hypocholesteremia of man the few facts available indicate that there is an increased excretion through the bile in some conditions like pernicious anemia and hemolytic jaundice. In experimental hypocholesteremia, no increase was noted. Landau and McNee (196), examining livers of man for the cholesterol content found that in hypercholesteremia the liver did not store cholesterol but rather in hypocholesteremia higher values were obtained. They consider the liver as an excretory organ in all animals, and that the difference is only a quantitative one. Normally the liver shows very small differences in its total cholesterol content (165) which agrees with Landau and McNee's (196) suggestion that the excretion is a rapid one.

An alimentary hypocholesteremia has been demonstrated by Cornell (84) in normal individuals shortly after ingestion of food and after histamine injections. The evidence was suggestive that the cholesterol leaving the blood went to the liver. He thought that the failure of this mechanism might actually suggest liver abnormality. In pernicious anemia patients this drop did not take place, but these patients had been on a liver diet for from 2 to 6 weeks. Experimentally the fall did not occur in dogs if the blood was diverted from the liver, but the cholesterol remained constant after eating and after histamine injections. Cornell thinks that the fall of cholesterol is associated with alimentation and occurs independently of any gastric secretion.

Summary

These findings with regard to the relation of exogenous and endogenous cholesterol to the bile cholesterol, indicate that two types of hypercholesteremia exist, namely, 1) a retention type in which less cholesterol is excreted through the bile as represented by pregnancy, nephrosis, and mechanical obstruction, and 2) a hypercholesteremia accompanied by increased excretion through the bile as seen after increase of cholesterol in the blood due to ingestion of large amounts of cholesterol or cholesterol rich food. In the former condition some change must have occurred in the liver as an excretory organ or in the cholesterol itself, while in the latter one may presume that a normal mechanism attempts to rid the body of the excess.

Hypocholesteremia, on the other hand, may be due to increased excretion through the bile or increased deposit in the liver and other organs. As explanation for this has been suggested an increased activity of the reticulo-endothelial system or a change in the colloidal state of the cholesterol. The equilibrium of cholesterol in the blood will be maintained if the excretory organ functions in an efficient manner.

CHOLESTEROL METABOLISM AND THE SPLEEN

A definite relation between the spleen, hematopoiesis and cholesterol metabolism has been established (273) (55) and contrary to the prevalent opinion that anemia and low cholesterol values occur together, in the anemia produced by splenectomy there is as a rule an increase of cholesterol in the blood.

Increase of cholesterol in the blood after splenectomy has been demonstrated experimentally by some in dogs (176) (206) (325), while others found no change (206) (58) and Goebel and Gnoinsky (142) a slight decrease after operation. Procedures which increase cholesterol in the blood in normal dogs as blood destruction (176) and administration of olive oil (206) cause a much more marked increase in splenectomized animals. This phenomenon has been explained by the decreased elimination of cholesterol by the liver (see above) and the absence of the spleen which normally participates in cholesterol elimination from the blood (206).

Hypercholesteremia after splenectomy has also been observed in rabbits (322) (244) and in guinea pigs (322).

An increase of cholesterol in the blood after splenectomy has been obtained in man in cases of hemolytic anemias and Banti's disease (176) (109) (238) (302) (93) (223). Denis (213), in two splenectomized cases of pernicious anemia, showed an increase of cholesterol in one and a decrease in the other.

The reports on the effect of splenectomy on the cholesterol level of the blood in man are not large, but the results scattered about in the literature are fairly uniform, although exceptions are reported.

It has been advocated that the spleen per se is not responsible for the changes occurring in the cholesterol metabolism. Soper (325) was unable to obtain any rise of the cholesterol in the blood of animals in which the spleen had been exposed to mesothorium rays, apparently destroying the cells of the pulp. He explains this result as due to the preservation of the reticulo-endothelial cells and that the rise after splenectomy is caused by the elimination of a part of this metabolic apparatus. Addis (7) also considered that the spleen influences the cholesterol metabolism but like Soper (325) attributed the change after splenectomy to the action of the peculiar endothelial phagocytic cells situated especially in the sinuses of the spleen and to a lesser extent in the capillaries of lymph glands and bone marrow.

THE RELATION OF THE CHOLESTEROL METABOLISM TO THE RETICULO-ENDOTHELIAL SYSTEM

The methods employed in the study of the cholesterol metabolism have been somewhat similar to the work on bile pigment formation recently reviewed by Rich (293). The attention is now directed with increasing persistency toward the reticulo-endothelial system as an important factor in the intermediary metabolism of cholesterol. This is of significance especially in the correlation of cholesterol metabolism to the anemias and the function of the hematopoietic organs. Investigations on the relation of the reticulo-endothelial system to cholesterol and lipoid metabolism in general have been divided mainly into 1) Morphological and 2) Physiological studies, the latter concerned chiefly with *a*) the determination of the level of cholesterol in the blood in response to the change in functional activity of the reticulo-endothelial cells, *b*) the amount of cholesterol in the blood entering and leaving the organs, and *c*) after removal of organs like the spleen and liver containing considerable amounts of this specific tissue.

Morphological studies

The ability of the reticulo-endothelial system to take up cholesterol, an electro-negative colloid, and other lipoids, is an elective process determined by the physico-chemical condition of these substances. Their presence in the reticulo-endothelial system has been reported by many observers both under experimental conditions and in disease of man.

In 1909 Ciaccio (81) noted large cells in the blood forming organs in normal conditions similar to those found in Gaucher's disease. He called them "Lecithin Zellen." The close relationship of the reticulo-endothelial system to the cholesterol metabolism was demonstrated by Anitschkow and Chalatow (12) (13) (14), who fed rabbits with cholesterol in oil and found subsequently that the cholesterol was present in the Kupffer cells of the liver and in cells of the bone marrow, lymph nodes and spleen, and that these cells also took up carmine and other vital stains as well as iron pigment. These observations have subsequently been confirmed by many observers (358) (192) (364) (189). The demonstration of cholesterol is made with special ease in the reticulo-endothelial system of the rabbit, due to the fact that in this animal cholesterol is not easily excreted (356). The deposit of fat in the spleen, however, is apparently a universal phenomenon, found in many animals as indicated by a review of this subject by Krause (189).

Deposit of lipoid substances, mixtures of cholesterol and other lipoids (266), has been demonstrated also in starvation both in the spleen (325) and the liver (309) (17). The increase of the lipoids is explained by Okuneff (266) as depending upon the hypercholesteremia found in starvation due to katabolic processes. Kusunoki (190) pointed out that it may be found after other kinds of cell destruction. The increase of cholesterol is not derived totally from the subcutaneous fat since the latter has been shown by Abderhalden (1) to be poor in cholesterol.

Small amounts of lipoids in the reticulo-endothelial cells of the spleen of normal rabbits have been demonstrated (266) while Eppinger (110) was unable to demonstrate lipoids in the reticulo-endothelial systems of man under normal conditions.

In pathological conditions of man, as diabetes (320) (222), however, lipoids are present in the reticulo-endothelial system, and often to a large extent. Wahl and Richardson (350) suggested that one may have a system disease, not of the hematopoietic organs as such but of the reticulo-endothelial system cells, and most striking in the hematopoietic organs because of the prominence of these cells in them. They concluded that the reticulo-endothelial system which controls the normal disposition of the lipoids of the body may be so seriously involved that the cells which normally dispose of the lipoids are unable to do so, resulting in a lipoid infiltration of other cells also as the parenchyma of the liver. In these accumulations in man, they think there may be a predisposing susceptibility of the reticulo-endothelial system and a disturbance in the lipoid metabolism, which may be manifested by a lipoidemia, and that it only requires some toxic or other injury of a part or all of the system to lead to a local or general accumulation of lipoid substances.

A system disease of the reticulo-endothelial system of infants with deposits of lipoid material was first reported by Niemann (260) and subsequently confirmed by others (50) (267).

Piney (275) considers that in pernicious anemia the liberation of lipoids from the destruction of red blood cells is the direct cause of the intense fatty changes found in the liver and other organs in this disease, i.e. both the haemosiderosis and the adiposis of the liver results from the storage of the products of destruction of erythrocytes. He states:

> "It is even probable that the apparently well nourished state of most sufferers from pernicious anemia depends upon the storage of the excessive amounts of phospholipins and fat liberated by the intense hemolysis. We have, therefore, to presume that the difference between normal hemolysis and that occurring in pernicious anemia is only a quantitative one."

He also suggested that if the hemolysis of pernicious anemia were due to some unknown toxin it would scarcely be likely to result in stimulating the normal mechanism for storage of fat, and indeed it would hardly be probable that normal products would result from the lysis.

Kusunoki (190) in many instances was able to correlate the presence of doubly refractile substances and other lipoids in pathological spleens with the amount of cholesterol in the blood. In one case, however, with high cholesterol values in the blood, very little fat deposit was found in the spleen, and he thought that it may be due to a decreased activity of the reticulum cells. In two cases of pernicious anemia the lipoid cells in the spleen were abundant while in a child of six, with "pernicious anemia," he found very little. In eight cases of secondary anemia no increase of lipoids in the spleen was noted. This difference he suggested was due to blood destruction in pernicious anemia, and the increase of the lipoid cells is a response to the lipoid set free by hemolysis of the red blood cells. As a rule, doubly refractile substances were less in children than in the adult. From his work he came to the conclusion that the spleen participates physiologically in the lipoid metabolism in that the reticular and endothelial cells take up the circulating lipoids and those formed in loco and metabolize them, and that the spleen thus regulates the lipoids in the blood. He maintained that these lipoid cells had the same origin as the pigment cells of the spleen.

Zinzerling, however, (364) does not agree with Landau and McNee (196), Kusunoki (190), Rothschild (307) and Hueck (165), who claim that these cells have a special function in the intermediary cholesterol metabolism, but he suggests that the reticulo-endothelial system removes the cholesterol, like all other substances, from the blood when an excess is present, and returns it to the blood when it sinks below normal due to the excretion of cholesterol. Hueck (165) considers that hypercholesteremia and cholesteatosis are coördinated phenomena. In many instances, however, deposits of cholesterol may occur without increase of cholesterol in the blood (17) (90), and low values of cholesterol in the blood may be concomitant with increase of lipoids in the tissues (275). Conversely, hypercholesteremia does not always lead to deposits of cholesterol in the tissues (304). In obstructive jaundice with a hypercholesteremia, normal or subnormal values of cholesterol have been found in the organs. Consequently other influences are present.

Physiological studies

The methods of influencing the reticulo-endothelial system physiologically are comparatively crude, the results contradictory. The influence on the cholesterol metabolism of splenectomy and hepatectomy has already been discussed. With the spleen a considerable part of the reticulo-endothelial system is removed, especially in animals with a large spleen, but the temporary change obtained and the return to normal, after varying intervals, of the functions related to this system, are explained by the compensatory hypertrophy of the cellular elements in other parts of the body (191). The extent and probable size of this system becomes clear when it is realized that, besides the spleen and other tissues, the reticulo-endothelial cells are scattered throughout the liver and the bone marrow, the latter with a potential size, realized in diseases like pernicious anemia, second only to the skeleton, muscles, and blood (237).

The method used for studying this system of cells is by injection of colloidal substances or by so-called "blocking." The latter term is a misnomer because actual blocking or elimination of the functional activity is not obtained in the experiments reported, and if obtained, is probably incompatible with life. However, decrease or increase of functional activity may be elicited, and the reaction obtained depends upon the colloid used, the size of the dose, the number and duration of the injections, and the functional activity of the cells themselves. A positive result may be considered as proof of participation by the reticulo-endothelial system, while a negative result may mean either nonparticipation of these cells or an insufficient degree of either stimulation or depression.

In 1911, Chauffard, Richet, and Grigaut (73) suggested that because of its colloidal nature the variation in the cholesterol of the blood serum is related to the activity of cells as illustrated by the localized concentration of cholesterol in atheromata and xanthelasma. This conception of the relation of phagocytic activity of cells and the cholesterol content of the blood is also illustrated by the work of Christian (80) and Kipp (179). Christian showed that numerous polymorphonuclear cells in the lung during the stage of gray hepatization contained large amounts of fatty material which differed in some respects from the body fat in that it did not reduce osmic acid, a characteristic of cholesterol, while Kipp found that the cholesterol in the early stages of pneumonia was low in the blood.

The relation of the cholesterol metabolism to the functional activity of the reticulo-endothelial system in dogs has been studied recently by Leites (205) using various colloidal substances. After injections of colloidal silver or olive oil emulsion the cholesterol decreased from 30 to 50 per cent in 10 minutes with a return to normal in 1 to 2 hours. Less cholesterol was found in the hepatic, femoral and splenic vein after a moderate number of injections indicating that the decreased amount in the blood coincided with an increased absorption of cholesterol by liver, spleen and bone marrow (205). The colloidal behavior of cholesterol was further demonstrated by determining the amount of cholesterol in the blood entering and leaving the lungs (204). A considerable part of cholesterol was deposited in the lungs, whether obtained from alimentation or after the intravenous injection of colloidal solutions of cholesterol. This is of interest as Kawamure (175) from morphological studies in dogs found cholesterol deposits in the epithelial cells of the bronchioles, and in both dogs and rabbits many cholesterin-rich cells in the sputum. The behavior of colloids and their deposition in the lungs as well as in other organs rich in phagocytic cells has been pointed out by Drinker and Shaw (100).

A fall in cholesterol after intravenous injections of colloidal substances has also been demonstrated by Beumer (46) in rabbits, and Goebel and Gnoinsky (142) in dogs. This reaction is probably a universal response as may be deduced from the findings of Cashin and Moravek (69). A colloidal suspension of cholesterol and lecithin injected into cats instead of increasing the cholesterol in the blood caused a drop from 20 to 60 per cent. Analysis of lung, liver and spleen showed that the cholesterol content had increased enormously in the lung and other organs and that cholesterol was present in endothelial cells.

As evidence of a decrease of the functional activity of the reticulo-endothelial system, Leites (205) cites the prevention of a normal fall of cholesterol in the blood after administration of olive oil in animals after "blocking" the reticulo-endothelial system. Ssokoloff (328) giving daily collargol injections to dogs and rabbits found a slight hypercholesteremia, more prominent in rabbits than in dogs. This has been explained as due to injury of the liver (142). That frequent administration of colloidal silver will injure the reticulo-endothelial system and decrease its functional activity has been shown by Muller (254).

On the other hand, Rosenthal, Moses and Petzal (305) report that in spite of intensive "blocking" with ink or iron or both together in normal and splenectomized animals, the serum cholesterol remained practically unchanged and only from time to time showed a tendency to a lower level. Artom (22) in an isolated liver could not determine any influence of "blocking" with collargol. He comes to the conclusion that either the method of "blocking" is without effect physiologically or the reticulo-endothelial system is without influence on the cholesterol metabolism. He feels certain, however, that the spleen participates in cholesterol metabolism but that its influence can be substituted by other organs.

The injection of colloids in dogs with their reticulo-endothelial system reduced by splenectomy modified the cholesterol level in a variable manner. Less decrease of cholesterol in the blood than normal has been reported (142) while the alimentary hypercholesteremia produced by cholesterol and olive oil was of smaller extent although there was no deficiency in absorption (205).

The results of the injection of colloids on the level of cholesterol has been variously interpreted. Leites (205) from extensive studies sums up his findings with regard to the reticulo-endothelial system and the cholesterol metabolism by pointing out that injection of electronegative metal hydrosols over a period of time increases the absorption or the functional activity of the reticulo-endothelial system of the spleen, liver and the bone marrow for cholesterol, and increases possibly also their function with regard to the metabolic processes and the change of the absorbed cholesterol. This increased functional activity of the reticulo-endothelial system is due to a stimulation and proliferation of the reticulo-endothelial cells. That stimulation occurs was verified by Leites (205) by microscopical examination of the organs of the experimental animals. Henning (156) attributed changes of cholesterol in the blood to changes in the permeability of the spleen, while Beumer (46) also considered that the drop of cholesterol in the blood after injections of colloids, without evidence of excretion in the bile was due to a hyperactivity of the reticulo-endothelial system. He suggested that this may be the true explanation of hypocholesteremia. However, a change may occur in the colloidal state of the blood by injection of colloids (46) (205) and this change may facilitate the subsequent removal of the cholesterol from the blood by the activity of the reticulo-endothelial system cells. Handowsky (151) has demonstrated that the stability of cholesterol as a colloid depends upon its union with certain fractions of proteins. Eufinger (115) gave evidences to show a change of the colloidal state of cholesterol in pregnancy. Deike (90) found that after injecting cholesterol intravenously with proteins there was a greater increase of the cholesterol in the blood which he did not attribute to the cholesterol itself but upon the changed quality and condition of the medium. The protein bodies seemed to decrease the resorption of the cholesterol and therefore increased its effectiveness. The increase of cholesterol in rabbits after feeding liver he also attributed to the proteins. With liver feeding more atherosclerotic changes were obtained than after pure cholesterol feeding. The mechanism of this he felt was not clear, but it seemed evident that the effect was not a chemical one but physico-chemical.

Another hypothesis put forward is that the spleen (3) (142) or the reticulo-endothelial system (45) synthesizes cholesterol and that variations may be explained by increase or decrease of synthesis. Authors agree, however, that the reticulo-endothelial system is an important factor in cholesterol metabolism.

CHOLESTEROL SYNTHESIS

The methods employed for elucidating the important problem of cholesterol synthesis by the animal organism have been: 1) determinations of the total cholesterol content of animals, at various stages of development, fed diets containing no cholesterol or known amounts of this substance, 2) balance experiments, i.e., determinations of the intake and output of cholesterol in animals, infants and adult man in health and disease.

From a comparison of the cholesterol content of eggs and newly hatched chickens Ellis and Gardner (102) and Beumer (44) concluded that in the development of the chick there was no synthesis. From similar experiments Thannhauser and Schaber (342) concluded that there was a synthesis, while Mendel and Leavenworth (240) thought that the cholesterol was utilized as it diminished during development. A change of the cholesterol during the development of the chick from free to cholesterol esters was shown by Mueller (250).

A comparison of the cholesterol content of the body of newly hatched chickens (136), rats (197) and mice (96) with animals of variable ages fed different kinds of food indicated that cholesterol is probably not synthesized and if synthesized this occurs only with difficulty. However, Dezani and Catorelli (97) kept white rats alive for 10 weeks on an extracted diet. Their cholesterol content was roughly double that of controls killed at the beginning of the experiment indicating synthesis. This was confirmed by Randles and Knudson (284) and Channon (77) in rats and by Beumer (45) in dogs. Channon (77) in well controlled experiments showed that rats fed from the weaning time until they had reached 100 grams in weight on a cholesterol free diet, had an increase in their cholesterol content from 100 to 220 mgm. Beumer (44) also demonstrated that in addition to a negative balance in infants there was a considerable increase of cholesterol in the growing brain and concluded that synthesis must take place.

So-called balance experiments, that is, comparing the cholesterol intake with the output in the feces, have been done on various animals, as well as infants and adults in health and disease.

Already in 1892 Jankau (169) attempted experiments on the balance of cholesterol. He found that when cholesterol was fed to rabbits and dogs only a part could be recovered from the feces. This was confirmed in rabbits (98), dogs (194) (183) (103) and cats (103).

Thus the early workers agreed quite uniformly from the results of balance experiments, that cholesterol can not be formed by the animal organism, and if the cholesterol is excluded from the diet none is excreted, the organism apparently conserving its supply (104). This contention has subsequently been disproved both in animals and man.

Among the first to submit evidences of cholesterol synthesis in man were Gamble and Blackfan (134). They demonstrated that in several normal infants the cholesterol output exceeded the cholesterol intake from 1.3 to 3.4 times over a period of three days This was interpreted as indicating synthesis. A negative cholesterol balance in infants has also been obtained by Beumer (43), with cholesterol-rich as well as poor diet. Beumer concluded that the cholesterol in the diet is excreted, and that a quantity which is a product of the endogenous cholesterol metabolism is excreted in excess.

The infant offers peculiar advantages for balance experiments because of the uniform diet and the excretion of the cholesterol unchanged. Adult man offers greater difficulty because the varied composition of the food, the possible storage of cholesterol in the body, and the change in the intestine of cholesterol to coprosterol.

From the early work of the English investigators, Ellis and Gardner (106), cholesterol synthesis in healthy adult man was denied. They observed, however, that an attack of influenza with rapid loss of weight, caused the output of cholesterol to exceed the intake. Later, Gardner and Fox (137) in eight adult subjects found that the fecal sterol output was about 2 to 5 times greater than the intake, indicating that the adult body must be capable of synthesizing cholesterol. Channon (77) criticized their results and thought that no rigid conclusions could be drawn from these observations as to cholesterol synthesis unless knowledge existed as to the function of the cholesterol stored in the various organs in the body. If the diet is poor in cholesterol the reserve supplies in the liver, adrenals and other organs might be called upon to make up the deficiency. Hence, unless experiments were carried out over a prolonged period, the possibility of the effect being due to cholesterol already stored in the body cannot be eliminated. A second objection raised by Channon is that bacterial synthesis of sterol in the large intestine may be the cause of the large excess of excretion over intake.

Thannhauser (341) has shown that a positive balance can be obtained in man with food low in cholesterol and that the minimum requirement for the adult is low.

A few determinations of the cholesterol balance in man in disease are found in the literature. Rosenbloom and McKelvy (300) studied a patient with hemolytic jaundice who was receiving a diet containing 5.22 grams of cholesterol determined by the method of Windaus. The cholesterol obtained in the feces was 12.27 grams, giving a negative balance of 7.05 grams. Beumer (44) in a series of cases fed for 8 to 10 days on the same diet in which cholesterol had been determined, showed that a healthy person had a negative balance of 0.081 grams. Three cases of pernicious anemia, contrary to expectations, showed a negative balance of −0.025, −0.119, −0.207. Beumer expressed the opinion that in a disease with a chronic destruction of cells rich in lipoid material and diminished cholesterol in the blood one ought to expect an increased negative balance. This was realized to a moderate degree in one case of pernicious anemia only. He realized that remission, crises, a stationary condition may influence cholesterol metabolism. No data are given to indicate the condition of the patients, except that they were "at a standstill showing no progress." However, in pernicious anemia Reicher (280) found an increase of cholesterol in the stools. The general fat metabolism is apparently not disturbed in pernicious anemia as the fecal fats were normal while nitrogen elimination was increased (174).

In amyloid and genuine nephrosis there was a tendency to cholesterol retention (44). A positive balance was obtained with foods rich as well as poor in cholesterol. In a case with common bile duct obstruction there was a negative balance of 0.035 gram, all of which can be accounted for by the food cholesterol which was not absorbed and a small additional amount from the intestinal secretion and epithelium.

From the above one may conclude that cholesterol can be synthesized by the organism both in animal and man. It is also evident that in contrast to our knowledge of the nitrogen metabolism the data on the cholesterol metabolism and balance in health and disease are, to say the least, fragmentary.

THE RÔLE OF VARIOUS ORGANS IN SYNTHESIS

Three organs, namely, adrenals, spleen and liver, have been prominently associated by many investigators as participating in cholesterol synthesis.

Adrenals

The relation of the adrenals to cholesterol metabolism and synthesis was recently reviewed by Joelson and Schorr (172). From this review, discussing the various trends of thought, and from subsequent work, it is evident that the adrenals are not the chief factor in cholesterol synthesis.

Spleen

The importance of the spleen and liver in cholesterol metabolism has been stressed by Aschoff (25). Proofs cited, mainly by French workers, for the participation of the spleen in cholesterol synthesis have been obtained mainly from autolysis of the organ. Aseptic autolysis (3) (229) at first increased the cholesterol, while subsequently a decrease was demonstrated. It has been claimed that *in vivo* this synthetic power of the spleen depends upon the normal function of digestion. Injection of hydrochloric acid into the duodenum of dogs increased the cholesterol in the arterial blood 100 per cent (4) (199) (290). This did not occur in splenectomized dogs and rabbits, except when splenic extract was injected or after transplantation of the spleen (6). Apparently the spleen as such is not responsible for the changes observed in the cholesterol, but a substance produced by the spleen (5). Rémond, Colombiès and Bernardbeig (290) obtained a rise also in splenectomized dogs after introduction of hydrochloric acid into the duodenum and they concluded that the spleen was not essential for this reaction. In clinical conditions with hyperacidity, hypocholesteremia has been reported which may be influenced by anti-acid medication (170).

Liver

Autolysis of the liver of normal (2) (351) and starved (22) animals has resulted in an increase of cholesterol, while Beumer (46) and Artom (19) could not demonstrate an increase if infection was excluded. Partial extirpation of liver in rabbits and dogs (328) did not influence the level of cholesterol in the blood to any appreciable extent. Thus the investigations of the relation of cholesterol synthesis to adrenals, spleen and liver are contradictory and the conclusion may be drawn from the data at hand that all these organs may participate in some unknown way in the synthesis and regulation of the cholesterol metabolism, but that at present no data are available connecting it with one definite organ.

SOURCE AND FATE OF CHOLESTEROL IN THE ORGANISM

With proofs of the synthesis of the cholesterol in the body the question arises as to the source and identity of the building stones as well as whether cholesterol is oxidized or destroyed in the body.

Source of cholesterol

Since Lifschütz (213) (215) showed that cholesterol can be obtained from oleic acid by oxidation, various types of experiments have been cited to support the theory of the relation between fatty acids and cholesterol. Addition of triolein to the blood of an isolated liver with an artificial circulation increased the cholesterol (208), while in autolysis experiments on the liver the production of cholesterol has been increased by addition of oleic acid (20) and in the spleen by sodium oleate (5). The importance of neutral fat and fatty acids as building stones in cholesterol synthesis has been emphasized by many investigators (5) (72) (75) (203) (342) (357). Increase of cholesterol and decrease of lecithin have been observed in human organs undergoing autolysis (352) but this has not been confirmed (247). Others claim that fatty acids, lecithin, and cholesterol can change into each other (357) (203). Terroine (338) disclaimed any relation of the fatty acids to cholesterol synthesis. He thought that there was a regulatory mechanism which mobilized cholesterol to keep it in constant relation to the fatty acids.

Beumer and Lehman (45) suggested that cholesterol synthesis possibly takes place in the entire reticulo-endothelial system from intermediary food products which are not ether soluble. Wacker (345) found an unsaponifiable substance which accompanied cholesterol in the organs. Hueck (165) suggested that perhaps this substance furnishes the building stones for cholesterol.

There is no doubt that cholesterol can be synthesized in the animal organism. What part or any the exogenous cholesterol takes in this synthesis is unknown as apparently all is excreted. The building stones of cholesterol have not been identified, although various substances have been suggested, primarily fatty acids.

Destruction of cholesterol

Whether cholesterol is destroyed in the body is uncertain. Mendel and Leavenworth (240) gave some evidence in support of its being burned. Chalatow (72) also believes that the body is capable of oxidizing cholesterol so that large amounts in the food are neither excreted nor deposited but burned. Destruction of cholesterol by the liver (216) and lung (262) (289) has been suggested.

However, the methods employed are criticised by Beumer (46) who considered that differences between the amount of cholesterol in the blood entering and leaving an organ, of differences between cholesterol in the blood and the bile, cannot be taken as indicating either synthesis or destruction as there is another way out for the cholesterol, namely, the tissues. Experiments of this type give us a picture only of the shifting of cholesterol in the body.

Autolysis of spleen (3) (229), kidney, adrenals and thyroid (229) has showed a decrease of the cholesterol content which was interpreted as destruction. Low cholesterol values occasionally found in retention icterus have been explained on pathological destruction (304) and hypercholesteremia to decreased destruction (149) (268).

In starving dogs, Beumer (46) demonstrated that cholesterol neither increased nor decreased, showing that neither synthesis, because of absence of building materials, nor destruction took place. He concluded that an oxidation of cholesterol is questionable and that as for destruction on a large scale there is no definite proof.

Investigators concerning themselves with the destruction of cholesterol naturally have attempted to identify the intermediary products. Chemically evidence of an oxidation of cholesterol to bile acids has been presented by Windaus (362) (363) and Wieland and Weil (361). Some investigators (87) (214) obtained an increase of bile acids after the administration of cholesterol, while others (123) have been unable to demonstrate an increase.

However, Enderlen, Thannhauser and Jenke (107) in experiments on dogs with bile fistula kept them in a negative cholesterol balance for months on an intake of 130 mg. of cholesterol per day. They therefore concluded that the exogenous cholesterol, which, due to the lack of bile, was poorly absorbed and left with the stools, has nothing to do with the bile acids. It became even more improbable when it was taken into consideration that the bile acids excreted were about 10 times greater in amount than the cholesterol ingested. Thannhauser (341) in balance experiments on two women did not find any relationship begween bile acids and cholesterol excretion.

With the demonstration that cholesterol can be synthesized in the body the problem of the formation of bile acids changes and the theoretical supposition that bile acids are formed from cholesterol loses its support as both bile acids and cholesterol may be formed from the same unknown substance perhaps in the same place (46) (129).

Thus it is evident that destruction of cholesterol has not been proved. The increase or decrease of cholesterol in the blood may be explained in other ways than by decrease or increase of destruction of this substance, and as far as is known, cholesterol is the end product of the cholesterol metabolism, except for the change in the intestine to coprosterine, a hydrated cholesterol.

INTERNAL SECRETION AND CHOLESTEROL METABOLISM

An efficient regulation of cholesterol in the body analogous to the nitrogen balance has been postulated (43). Thus the intake and output will be equal whether cholesterol is abundant or insufficient, and under normal conditions very little storing of cholesterol takes place with a rich cholesterol diet, while with an insufficient diet the body protects itself against loss. The baffling obscurity as to this regulation is reflected in the vast amount of work undertaken to discover the mechanism regulating the cholesterol in the blood. Berberick (41) has suggested that hypocholesteremia may depend upon constitutional weakness of the endocrine system which is hereditary and familial, while Grigaut (149) maintained that the ability of the body to form cholesterol is increased in certain diseases by hormones.

Thyroid

In 1922 Epstein and Lande (112) in a series of cases with thyroid disorder found low values of cholesterol in the blood in hyperthyroidism and high values in myxedema. These findings have been confirmed (48) (154) while Castex and Schteingart (70) studying 24 cases of hyper- and hypothyroidism correlating cholesterol in the blood to the basal rate could not demonstrate any relation between increased combustion and the level of cholesterol in the blood. Epstein's (112) conclusions receive some support from experimental work. Removal of the thyroid gland in animals (22) (271) (291) (349) caused a considerable increase, while feeding of thyroid and injection of thyroid extract (212) caused a reduction of the cholesterol in the blood. Goldzieher and Hirschorn (143) found that the storage of cholesterol was increased by thyroid administration in Kupffer cells of the liver. Large doses of thyroid extract (212), on the other hand, caused an increase of cholesterol in the blood which is explained on mobilization of fat. However, in morphine intoxication both the basal metabolism and cholesterol are lowered (27) and in the later months of pregnancy high cholesterol values are concomitant with an increased basal metabolism, the latter thought to be due to the acidosis (152). Hueck (165) draws the attenton to beri beri which shows increased cholesterol in the blood, decreased oxidation and acidosis, while adrenalectomy in animals caused decrease of basal metabolism and increase of cholesterol in the blood. In young, actively growing infants the cholesterol values were much lower than in the adult (33) (264), while 50 per cent of individuals about 55 years of age showed a hypercholesteremia (239), probably depending upon physico-chemical changes in the cell membrane, decreasing its permeability.

It is evident that variations of the cholesterol level in the blood may occur with variations in the basal metabolism. Up to the present time, however, no constant relation has been demonstrated.

Adrenals

Removal of the adrenals in dogs (172) and rabbits (309) caused an increase of the cholesterol in the blood, while Grigaut (149) in dogs, and Ssokoloff (329) in man, after removal of one adrenal, could not demonstrate any increase. Injection of epinephrine did not influence the cholesterol level in the blood of dogs (172) while subcutaneous administration of adrenalin in rabbits (217) increased the cholesterol in the blood 2 to 4 hours after injection. A slight increase of cholesterol was noted in patients injected with epinephrine subcutaneously and intravenously (10) (167). Joelson (172) suggested the possibility that the internal secretion of the adrenals has some effect on blood cholesterol similar to the pancreas on blood sugar.

Pancreas

Mahler (224) observed that in ether anesthesia there was a rise of the cholesterol and glucose in the blood, and that this rise could be prevented if insulin was administered before the anesthsia. The cholesterol and glucose level, however, does not run parallel in pernicious anemia in which Gettler and Lindeman (139) found high sugar values and low cholesterol. Nitzescu and co-workers (261) (262) demonstrated that the normal deposit of cholesterol in liver and lung of dogs was prevented if the pancreas was removed. Insulin administered to normal and depancreatized dogs increased the deposit of cholesterol in the former, but brought it back to normal in the depancreatized animals. The amount of cholesterol in the liver in diabetic dogs has been found decreased (20). Insulin thus has a definite influence on the fixation of cholesterol in the tissues (216).

Pituitary

In 1916 Warthin (354), studying two cases of pituitary dystrophy, observed that a cholesterol infiltration or retention occurred. Moehlig and Ainslee (246) demonstrated an increase of blood cholesterol in rabbits after the administration of posterior pituitary extract injected for 10 days. They explain the result on the selective action of the pituitary secretion on mesenchymal tissues which are involved in the cholesterol metabolism. Pituitrin, however, does not alter the storage of cholesterol (143). Increased excretion of cholesterol in the feces has been reported in acromegaly (130).

It is clear that whatever the function of the internal secretions in the regulation of the cholesterol in the body, as yet no definite relation has been established.

CHOLESTEROL IN ANEMIAS

In certain clinical conditions, especially anemia, cholesterol shows a deviation from the normal indicating that in some way the metabolism of this substance is intimately related to the proper functioning of the hematopoietic organs.

It has been stated that anemia is the chief condition in which low values of cholesterol are found (65) (256) (317) (332) (334). This statement is occasionally modified to the effect that the decrease of cholesterol in anemias is not marked unless red blood cells and hemoglobin have declined below 50 per cent of normal (223).

In reviewing the literature describing the work on blood cholesterol, especially in pernicious anemia, one is struck with the variability of the results obtained by different observers. This fact has already been commented upon by Köhn (187). To obtain any understanding of the cholesterol metabolism in anemia the material available has been analysed in secondary anemia and the so-called hemolytic anemias.

Cholesterol in secondary anemia

The study of the cholesterol level in the blood in secondary anemia is fragmentary. In most instances only one determination has been made on each case and 60 per cent are unaccompanied by blood counts.

One hundred and nine cases with actual figures of cholesterol have been analyzed. Of these, 5 were chlorosis (15) (42) (113) (312), 2 aplastic anemias (15) (140), 2 were due to Bothriocephalus latus (55) (92), 15 were secondary to carcinoma (42) (53) (55) (92) (145) (303) (330), 21 leukemias (34) (35) (42) (55) (92) (145) (223) (312) (330) (335), 15 splenic anemias or Banti's disease (15) (92) (110) (140) (223) (238) (303) (312), 18 secondary to hemorrhage (55) (92) (118) (223) and 31 were due to various causes (34) (53) (55) (176) (187) (188) (223) (238) (294) (330) (334) (335) and in some instances classified only as secondary anemia.

TABLE 1

Cholesterol in secondary anemias

DIAGNOSIS	NUMBER OF CASES	RELATIVE AMOUNT OF CHOLESTEROL IN THE BLOOD			NUMBER OF CASES WITH RED BLOOD CELL COUNT	DEGREE OF ANEMIA	
		Above normal	Normal	Below normal		Erythrocytes below 2,500,000	Erythrocytes above 2,500,000
Chlorosis	5		2	3	2		2
Aplastic anemia	2	1	1		2	1	1
Bothriocephalus anemia	2			2	2	1	1
Secondary anemia due to carcinoma	15	1	8	6	4	3	1
Lymphatic leukemia	6		3	3	3	1	2
Myelogenous leukemia	15		2	13	4		4
Splenic anemia or Banti's disease	15		5	10	9	1	8
Anemia secondary to hemorrhage	18	12	4	2	6	3	3
Secondary anemia due to divers causes	31	4	14	13	11	1	10

The result of this analysis is set forth in table 1 where the number of cases according to the standard set by each individual author have been classified as having normal cholesterol values, or values above or below normal.

Of the 11 cases with a red blood cell count below 2.5 millions, 6 showed cholesterol values below normal and 5 were within normal limits.

Some important facts were revealed by this analysis. Normal or high cholesterol values were present in severe aplastic anemia. In Bothriocephalus anemia with low initial values there occurred a considerable increase of the blood cholesterol as soon as the worm was delivered (55). The increase of cholesterol preceded the rise of the erythrocytes. In anemia due to carcinoma, 6, or 40 per cent, showed subnormal cholesterol values and of these all but one, in which the location was not stated, had carcinoma of the esophagus or stomach. Gorham and Myers (145) in some of their cases with carcinoma of the stomach and oesophagus found somewhat low values in the later stages (about 120 mgm. per 100 cc. of blood against a normal average of 150 mgm. per 100 cc.). In gastro-intestinal conditions as ulcer or colitis the cholesterol values were within normal limits. Of the 15 cases of myelogenous leukemia, hypocholesteremia was present in 13 although the anemia was slight when recorded. The white cells ranged from 110,000 to 220,000 per cubic millimeter. In the 15 patients with Banti's disease, 10, or 66.6 per cent, had low cholesterol concentration in the blood while the red blood cells varied from 2.6 to 6.2 millions per cubic millimeter in the six cases recording blood counts. Only two were below 3 million erythrocytes per cubic millimeter, consequently the decrease of red blood cells was in most instances not extreme. In three cases with splenectomy a marked hypercholesteremia was present in 2, and normal values in one (223). The number of red blood cells in the one case reported was normal but with a low color index (0.62).

A systematic study of the cholesterol and the other lipoids after hemorrhage in man has been made by Feigl (118) in severe post-operative hemorrhage in comparatively healthy men, hematemesis, severe menstrual bleeding, and hemoptysis due to tuberculosis. Unfortunately no blood counts are recorded, so that the severity of the anemia is unknown. The striking fact about his report is the uniform increase of cholesterol evident on the first day after the hemorrhage in most cases and very marked after 48 hours. At the end of the first week hypercholesteremia persisted although to less extent than on the second and third days. The amount of the lipemia was modified by the general condition of the patients. The rise observed was less in undernourished individuals, and more cholesterol and lecithin were mobilized in severe menstrual bleeding than from a single hemorrhage. In nephritis, bleeding caused an addition only of neutral fat if the cholesterol was already increased in the blood. McAdam and Shiskin (22) reported two cases with low values. One patient had metrorrhagia and one "hemorrhage," with 2.0 and 0.9 millions red blood cells per cubic milimeter respectively.

After bleeding, the lipoids were also increased in the blood of rabbits (56) (59) (118) (161) (244) (314). This lipemia was observed by Horiuchi (161) to be present on a practically fat free diet, while Boggs and Morris (59) noted that the animals became very emaciated. They suggested that the great loss of tissue protein might have some influence on the abnormal fat metabolism.

The increase of cholesterol in severe anemias due to bleeding is in sharp contrast to the cholesterol content in many other anemias. The mechanism of this lipoidemia has been variously interpreted as being due to lack of red blood cells and decreased oxidation (59), decrease of lipase and consequent decrease of metabolism of lipoids (161) (314), and mobilization of fat from the tissues and especially the bone marrow (56) (59). Bloor (56) considered that in hemorrhage there was an outflow of lipoids into the blood in larger quantities than the normal mechanism can dispose of at once, while Horiuchi (161) thought that the outflow was diminished. The cause of this sudden mobilization of lipoids Bloor (59) suggested to be due to cellular inanition which undoubtedly exists. The displacement of fat by the blood forming tissue he considered an interesting possibility.

Another explanation of this phenomenon has been offered by Fishberg and Fishberg (119) (120). They confirmed the increase of fat and cholesterol in the blood of rabbits with hemorrhagic anemia. The total proteins, however, were decreased, and there was a shift in the albumin-globulin ratio in favor of the latter. This picture is also found in the so-called Epstein's nephrosis (111) in which the cholesterol is greatly increased. Fishberg and Fishberg concluded that the increase of the cholesterol and the fat after hemorrhage is due to the loss of serum protein and may be considered as a compensatory phenomenon for the purpose of maintaining the colloidal osmotic pressure in the blood at a normal level. This fat was mobilized from the fat depots of the body (119) (120) (244) and the lipoidemia after hemorrhage was similar to the ones seen in nephrosis in which disease Hiller, Linder, Lundsgaard and van Slyke (160) have shown that there is no impairment in the burning of the fats.

Confirmatory evidence of above hypothesis has recently been reported by Fishberg (121), who noted that the osmotic pressure in lipemic blood was higher than in blood diluted to the same concentration of protein, and this difference became apparent at the same time as the total lipoid content of the blood started to rise.

Bloor and McPherson (55), and McAdam and Shiskin (223) state that there does not seem to be any characteristic difference in the blood lipoids in different types of anemia, while Köhn (187) emphasizes that all investigators have found low values in all hypochrome anemias and that his own determinations confirm this. It is evident from the analysis of this miscellaneous group of secondary anemias that one is not justified in concluding from the data at hand that cholesterol is low in all cases of secondary anemia.

Cholesterol in the so-called hemolytic anemias

In the so-called hemolytic anemias, primarily congenital hemolytic icterus and pernicious anemia, cholesterol has been assumed to be intimately related to the disease process since the discovery by Ransom (285) that saponin hemolysis could be prevented by cholesterol, and by Noguchi (263) and Keyes and Sachs (195) that it acted in the same way with cobra poison *in vitro*. Morgenroth and Reicher (248) and others (131) (278) then proved that cholesterol was able also to prevent hemolysis *in vivo*, and Meyer (242) demonstrated that the sensitiveness of the erythrocytes to saponin hemolysis depended upon their cholesterol content. Considerable work has been devoted to the relationship of cholesterol to hemolysis. This work was recently reviewed by Campbell (65).

Hemolytic jaundice. In many cases of icterus, especially of the retention type, the cholesterol in the serum is increased. In 1911 Chauffard, Laroche and Grigaut (74) observed that in three cases of hemolytic icterus no augmentation of the cholesterol in the blood could be demonstrated. This was verified by Rothschild and Felsen (312) who attempted to correlate icterus and the cholesterol content of the blood.

Since familial hemolytic jaundice became recognized more widely as a disease entity, several determinations on cholesterol have been made and in some instances reported without any figures, but said to be decreased below normal (258) (265) (269).

From the literature 37 cases of hemolytic jaundice with cholesterol determinations on the blood have been collected (15) (34) (35) (75) (85) (110) (117) (140) (176) (223) (238) (272) (303) (332). Of these, only 11 report red blood cell count and only 5 more than one determination (117) (223). In analyzing these 37 cases it was found that 25, or 67.5 per cent showed hypocholesteremia. Of the remaining 12, two showed hypercholesteremia (117) (140) while the other 10 were within normal limits (34) (35) (75) (117). Cholesterol values in the plasma below 50 per cent of normal were found by the author (253) in a case of hemolytic jaundice. After splenectomy the cholesterol remained low for 38 days during a stormy convalescence and with slight improvement of the anemia. McAdam and Shiskin (223) have also determined the cholesterol content of the blood in relation to splenectomy. After splenectomy there was a gradual increase of cholesterol in the blood which resulted in hypercholesteremia or normal cholesterol values with red blood cells between 5.2 and 6.7 millions per cubic millimeter.

An interesting observation has recently been made by Leites (207) suggesting that the acid-base balance may be of importance for the regulation of the cholesterol in the blood. In splenectomized dogs he observed that the destruction of acetone and the ketone bodies was decreased and that this was most prominent in explaining the hypercholesteremia occurring some time after splenectomy. Only one case of acquired hemolytic jaundice with 117 mgm. of cholesterol in the blood and 4.0 million erythrocytes per cubic millimeter and 80 per cent hemoglobin, has been reported (15).

From an examination of these rather incomplete data it is striking how frequently hypocholesteremia is encountered in hemolytic jaundice in spice of the fact that, comparatively speaking, the anemia is not severe. In no single instance were the red blood cells, when reported, below 50 per cent of normal.

This behavior of cholesterol is of so much more interest, because as a rule the patients with hemolytic jaundice are in fairly good health and nutrition, refuting to some extent the supposition that low cholesterol values depend upon debility and lack of vitality.

Pernicious anemia. Determinations of cholesterol in the blood plasma or serum of 172 cases described as pernicious anemia have been analyzed (15) (34) (35) (39) (42) (54) (55) (85) (92) (117) (140) (145) (174) (176) (178) (184) (187) (223) (238) (255) (270) (294) (303) (312) (317) (330) (332) (335) (359). This covers the greater part of the examinations recorded and available. Of these 172 cases, 120 had only one cholesterol determination, 69 of which were accompanied with no data for red blood cells and hemoglobin. In the remaining 51 cases with one cholesterol determination, the results of one examination of red blood cells and hemoglobin were recorded. This leaves 52 cases, of which number 23 had two determinations of cholesterol, while 29 patients were studied in somewhat more detail (55) (140) (145) (178) (187) (270) (359).

TABLE 2

The relation of the cholesterol level of the blood to the degree of anemia

ERYTHROCYTES	NUMBER OF CASES	RELATIVE CHOLESTEROL VALUES IN THE BLOOD			SUBNORMAL VALUES
		Above normal	Normal	Below normal	
millions per cu. mm.					*per cent*
0–1	21	2	4	15	71.4
1–2	47	6	12	29	61.7
2–3	22	2	10	10	45.4
3–5 or over	11	4	4	3	27.2

In 114 cases, especially recorded in more recent reports, cholesterol determinations were done either on the serum or the plasma.

The initial values of cholesterol in the 172 cases studied, according to the standard of normal set by the respective authors, were above normal in 18, within normal limits in 47, and below normal in 107, or 62.2 per cent. The red blood cell counts were recorded in 101 cases. The relative cholesterol content in the blood of the various groups classified as to the severity of the anemia is shown in table 2.

A reduction of 50 per cent of the red blood cells per cubic millimeter were seen in 84 out of the 101 cases in which blood counts are recorded. Of these 84, 46, or 54.7 per cent, had lower cholesterol values than normal.

The number of cholesterol determinations made on the 101 cases with blood counts recorded was 196. The percentage of subnormal, normal and high values of cholesterol in relation to all the blood counts are set forth in table 3.

TABLE 3

The relation of the cholesterol to the erythrocyte concentration of the peripheral blood

ERYTHROCYTES	NUMBER OF DETERMINATIONS	RELATIVE CHOLESTEROL VALUES IN THE BLOOD		
		Above normal	Normal	Below normal
millions per cu. mm.	*per cent*	*per cent*	*per cent*	*per cent*
0–1	13.7	1.0	2.5	10.2
1–2	37.4	3.6	13.9	19.9
2–3	28.5	2.0	13.7	12.8
3–5 or over	20.4	6.7	9.2	4.5
Total..........	100.0	13.3	39.3	47.4

TABLE 4

The relation of the cholesterol level to the course of the anemia

CHOLESTEROL LEVEL	NUMBER OF CASES	ERYTHROCYTES LEVEL—NUMBER OF CASES		
		Stationary	Increased	Decreased
Stationary	11	3	5	3
Increased..............................	17		15	2
Decreased..............................	17		10	7

In table 4 the relation of the cholesterol in the blood to the course of the disease as evidenced by the decrease or increase of the erythrocytes in the blood is set forth. Twenty-nine cases with the number of cholesterol and red blood cell determinations ranging from 3 to 8, and 16 cases with 2 determinations, have been analyzed.

This table shows that with a stationary cholesterol level the red blood cells may remain stationary or show increase or decrease, while if the cholesterol increases the red blood cells are apt to increase. A lowering of the cholesterol level may be accompanied by a rising blood count.

This lack of correlation in the relation of the number of red blood cells and corresponding hemoglobin values and the amount of cholesterol in the blood has been commented upon by various observers (42) (92) (187) (223). Others, however, claim that the number of red blood cells, that is, the anemia, is directly related to the low values of cholesterol (55) (317) (334). Bloor (55) suggested that the numerical decrease of red blood cells may play an important part because they participate in the metabolism of fats and cholesterol. Wesselow (359) and Beck (37) also concluded that there was a rough parallelism between the rise of the plasma cholesterol and the increase of the red blood cells, the highest red blood cell count per cubic millimeter corresponding to the highest cholesterol values.

The correlation of the concentration of red blood cells and hemoglobin and the cholesterol level of the blood would furnish a simple explanation of the decrease of cholesterol found in a certain number of cases of anemia and would cover all anemias due to any cause. It is difficult, however, to correlate the fact that pernicious anemia patients with red blood cells below one million per cubic millimeter may have normal or high values, while others with a blood containing more than 50 per cent of the normal numbers of erythrocytes show subnormal values.

The relation of cholesterol to blood transfusion in pernicious anemia has been studied by Denis (92) and Kipp (178). They could not find any parallelism between the blood cholesterol and the increase of red blood cells due to transfusion except in a patient that apparently was enjoying a remission (178).

To illustrate that the cholesterol level of the blood and the number of red blood cells bear little or no relation to each other, 10 cases of polycythemia may be cited (110) (176) (188) (223) (238) (280). Of these 3 showed hypocholesteremia and in one of these cases the cholesterol was very low, 74 mg. per 100 cc. (223). Five had values of cholesterol within normal limits, while two showed hypercholesteremia which led Pribram (280) to conclude that the increase of cholesterol protected the red blood cells from destruction and that polycythemia was due to a decrease of blood destruction. The reason for the increase of the cholesterol he suggested might be due to liver injury. Beumer and Bürger (42), however, found urobilin in the urine of polycythemia vera patients and therefore concluded that blood formation as well as destruction was increased. Köhn (87) attempted to correlate the stage of the disease to the cholesterol content of the blood. He found low cholesterol values in 4 of eleven cases studied with red blood cells below 1.0 million per cubic millimeter, and with increase of serum bilirubin. In a fifth case the cholesterol rose from 70 to 110 mgm. per 100 cc. concomitantly with a decrease of red blood cells from 1.1 to 0.8 million per cubic millimeter, the decreased bilirubin indicating a remission. However, the patient died. In another case with five determinations the cholesterol fluctuated between 101 and 126 mgm., a very narrow range, accompanied, however, by considerable fluctuations of the red blood cells between 3.3 to 2.1 millions per cubic millimeter, the lowest cholesterol value corresponding to the lowest red blood cell count. From these data he concluded that low cholesterol values are found at the height of exacerbation of the disease, while higher values but under normal were found in relative remission with normal values in complete remission.

The lack of correlation between the concentration of red blood cells and hemoglobin and the cholesterol level in the blood in pernicious anemia can be explained by the results obtained by the author (253) in a series of pernicious anemia patients. It was found that the cholesterol in the blood plasma was low in relapse but that a sudden rise to a higher level, which later increased and was maintained, occurred at the onset of the remission. This increase of cholesterol was concomitant with the reticulocyte response, apparently proportional to the intensity of the reaction and not dependent upon the form in which the active principle effective in pernicious anemia was administered, nor upon the number of red blood cells in the peripheral blood. Therefore normal or high values for plasma cholesterol with low red blood cell counts in pernicious anemia indicate that remission is taking place. This increase of cholesterol apparently did not depend upon an alimentary hypercholesteremia but upon the intermediary cholesterol metabolism, an opinion which has been concurred in by others (9) (359).

These results may explain the varying relationship of the cholesterol level to the degree of anemia in the disease pernicious anemia, but few facts are available to explain the low values found in relapse.

The theory has been advanced that hypocholesteremia depends upon the nutrition and strength of the patient, not the condition leading to anemia (42) (66). This opinion is expressed also by McCrudden and Sargent (231) who claim that low cholesterol values in the blood are due to low vitality.

Changes in plasma volume (94) (359) and abnormalities in the metabolism of simple fats (84) (140) (174) have been excluded. However, there is a tendency to overstorage and pathological infiltration of cholesterol and other lipoids in the active tissues (84) (164) (177) (275), while others have found decreased values (39) (196). Piney (275) considers that the normal mechanism for storage of fat is stimulated. In addition there is some evidence of a loss of cholesterol in the bile (34) and in the stools both in pernicious anemia (286) and in hemolytic jaundice (300).

The general opinion in the literature as to the importance of cholesterol in pernicious anemia is divided. That it is an antihemolytic agent used up against the disease process in pernicious anemia has been refuted by McNee (235). However, McNeil (236) thought that cholesterol, an antihemolytic agent, is an important factor in anemic conditions and that the lack in pernicious anemia is a permanent and progressive defect. Bloor and McPherson (55) concede the fact that cholesterol acts as an antihemolytic agent against certain substances, but state that there is no evidence to show that it protects against hemolysis by the fatty acids thought to be the agents for the production of human hemolytic anemias. Nevertheless, Bloor (53) feels that the low values for cholesterol in the plasma are not without significance in view of the part which cholesterol is said to play in protecting corpuscles from action of hemolytic agents. This opinion has also been voiced by Warden (353), Stern (332), Myers (256), Kipp (178), Pacini (270) Gibson and Howard (140) and Köhn (187), while Squier (327), Csonka (85) and Ridge (295) advance the opinion that the general disturbance of the lipoid metabolism of the body is the primary cause of the disease.

On the principle that cholesterol prevents hemolysis (248) Reicher (287) treated pernicious anemia patients with cholesterol and reported improvement but he did not think that cholesterol was a specific. Beneficial results were also obtained by others in pernicious anemia (67) (99) (114) (184) (270), and hemolytic jaundice (269) (272) and in other anemias (99). Pribram (279) (280) and Simon (323) obtained no results with cholesterol therapeutically in pernicious anemia, and x-ray anemias remained unaffected (99). Pringsheim (283) in a case of paroxysmal hemoglobinuria was able to prevent the hemoglobinuria by subcutaneous injection of cholesterol. That cholesterol is not a specific, although improvement can be obtained in anemias of the hemolytic type, may be concluded from the data at hand.

However, McAdam and Shiskin (223) point out that there is conclusive evidence of increased cholesterol in the plasma and decreased hemolytic activity. This has subsequently been confirmed by others (178) (303) (312). Kipp (178) thought that the fact that in two of his cases of pernicious anemia, treated with transfusion, the cholesterol remained low, indicated perhaps an increased utilization of this substance against toxic elements causing hemolysis. Neilson and Wheelon (259) and others (39) (281) have suggested that cholesterol acts as a protective and that this action in some measure is proportional to the content of cholesterol in the serum. This protection is considered as of a chemical nature. Rosenbloom and McKelvy (300) also discuss cholesterol as an antihemolytic agent, and suggest that hemolytic jaundice is due to a perverted cholesterol metabolism causing a lessened amount in the serum. They come to the conclusion that there is some relationship between the increased fragility of the red blood cells, the cholesterol content of the blood, and the spleen. Giffin (141) and McAdam and Shisken (223), however, showed that the increased fragility of the red blood cells before splenectomy remained unaltered after splenectomy, although the cholesterol rose above normal values.

That some relation exists between blood destruction and the amount of lipoids in the blood was suggested by Erben in 1902 (113). Experimentally it has been shown that destruction of red blood cells with hemolytic poisons increased the amount of cholesterol in the blood (235) (244) (346), bile (193) and feces (194). Eppinger (110), however, was unable to produce an increase of cholesterol with toluylendiamine in rabbits, while Bodansky (58) found the total cholesterol diminished in dogs made anemic with diazopropylhydrazine hydrochloride. With acetyl phenyl hydrazine variable changes were obtained. Dubin (101) in trypanosome anemia of dogs found the cholesterol of the blood decreased.

Wacker (345) also found that cholesterol in the fat was increased in carcinoma, chronic sepsis and in metabolic diseases as diabetes and in all *yellow fat* of man. It has been concluded that as a rule when body cells are destroyed (182) and in parenchymatous degeneration (335), cholesterol is increased in the blood and tissues (42). It is therefore evident that the low cholesterol values often found in the so-called hemolytic anemias are contrary to what would be expected in a disease where destruction of cells plays an important rôle.

A few suggestive reports of the relation of the lipoids to cell proliferation are available. Cholesterol (218) (296) has been claimed as an agent that can increase growth of cells. Kipp (179) pointed out the hypocholesteremia in acute infections as pneumonia. He found that the variation of cholesterol in the serum depended upon the activity of the leucocytes, as cholesterol was transported by them to the area of infection. The enrichment of cells of exudates in cholesterol has been shown by Halliburton (150). Empyema fluid with many pus cells contains two to three times more cholesterol than comparatively acellular fluid. In animals subjected to low barometric pressure experimentally, Sundstroem and Bloor (337) demonstrated that the lipoid phosphorus was decreased in the blood. They suggested that the enrichment of the erythropoietic organs with lipoid material might be the first phase of stimulation of these organs resulting from the low atmospheric pressure. There is also some evidence that cholesterol may be retained or perhaps deposited in the hyperplastic bone marrow of pernicious anemia (292). The possibility of the utilization of the lipoids in the formation of the enormous number of megaloblasts in the bone marrow of pernicious anemia must be thought of.

SUMMARY AND DISCUSSION

The question arises as to how an abnormality of the cholesterol level in the blood may be brought about. From the above review of certain aspects of cholesterol metabolism it is seen that variable results have been reported with regard to the relation of cholesterol in the food and the cholesterol in the body. The consensus of opinion seems to be that in herbivorous animals the cholesterol level can be raised or lowered in the blood by variation of the cholesterol in the diet, while in omnivorous and carnivorous animals an efficient regulatory apparatus exists and the increase or decrease is temporary. Thus in man the ingested cholesterol plays but a little part in the endogenous cholesterol metabolism and an abnormality of the cholesterol level in the blood is not to be looked upon as a decrease or increase of the mass of cholesterol but as an abnormality of regulation. The organs and cells mainly involved in the cholesterol metabolism have been defined, and among these the reticulo-endothelial system plays an important rôle, thus explaining the relation to some extent of the variations of cholesterol in diseases involving the blood and blood forming organs. Evidences have accumulated making it practically certain that cholesterol can be synthesized in the body, perhaps from fatty acids, although the building stones have not been definitely identified. Destruction of cholesterol in the body, at the present time, seems improbable. Variations in the cholesterol level of the blood and tissues have been associated with practically all endocrine disturbances, and the relation may become clear with further knowledge of the various internal secretions, their interrelations and function in the body.

In anemic conditions the cholesterol in the blood is decreased in a certain percentage of cases, more so in the so-called hemolytic anemias than those due to known causes. The low values of the blood cholesterol oftentimes seen in anemia have been ascribed to various causes, and among others to the decrease of the erythrocytes in the peripheral circulation. It is evident that other factors play a part as hypercholesteremia may be observed in severe pernicious anemia and in hemorrhagic anemia. Suggestive evidences have been given that in pernicious anemia the cholesterol level is closely related to the relapse and remission and that the rise of the cholesterol at the onset of the remission is called forth by the active principle effective in pernicious anemia. The mode of action of this principle on the cholesterol metabolism is unknown, as no data are available as to what happens to the balance of cholesterol at this stage of the disease. One may, however, speculate as to this mode of action. Evidences have been presented which indicate that low cholesterol values may be obtained by increasing the functional activity of the reticulo-endothelial system. An increase of the functional activity of the reticulo-endothelial system would explain the low values of cholesterol in the blood in the so-called hemolytic anemias in which the increased blood destruction and bile pigment formation point to an increased activity of this system of cells.

It certainly is not a mere coincidence that in pernicious anemia the blood destruction and bilirubinemia decrease at the onset of the remission, while cholesterol increases. A decrease of the functional activity of the reticulo-endothelial system would explain all these phenomena.

Some further evidence pointing to the close relationship between the activity of the hematopoietic organs and the level of cholesterol in the blood have been obtained by the author in experimental work on pigeons (252), in which an increase of cholesterol in the blood was closely associated with a decrease of the hematopoietic function, i.e., a decrease of the functional activity of the reticulo-endothelial system in the various organs. By correlating the functional activity of the reticulo-endothelial system and the level of the cholesterol in the blood, facts which now seem obscure may perhaps be explained. The hypercholesteremia found in many conditions associated with acidosis may thus be adequately explained on a decrease of the functional activity and permeability of cells. Hueck (165) emphasizes the importance of the acid-base balance by pointing out that the same organs regulating the acid-base balance also regulate the cholesterol. Many evidences point to a relationship between cholesterol retention and acidosis. Substances decreasing oxidation and administration of acids will cause increase of cholesterol in the blood and deposits in the tissues. This does not necessarily imply a change in the acid-base balance of the blood, but of the tissues, which normally may have a different acid-base balance. Various diseases with recognized acidosis also show a cholesterol retention. The disturbance of the acid-base balance may, perhaps, also explain the ease with which the cholesterol level may be disturbed in herbivorous animals. The regulation in these animals of the acid-base balance is not as efficient as in omnivorous and carnivorous animals.

The increase or decrease of the cholesterol in the blood is probably also associated with other phenomena. Thus the hypercholesteremia in hemorrhagic anemias and nephrosis has been explained on the lack of proteins in the blood and the influx of cholesterol and other lipoids for the purpose of maintaining the osmotic tension.

An interesting suggestion to explain the variations found in the blood has been advanced by Currie (86). He examined series of normal individuals and patients with carcinoma, and found that the cholesterol values were lowest for all individuals from November to January, and highest in the summer months. He thinks that seasonal variations may play some rôle.

Another possibility causing a decrease of the cholesterol in the blood which must be seriously considered is the lowering of the blood cholesterol because of its utilization by actively growing cells.

The change of the colloidal state of the cholesterol may also be a factor increasing or decreasing the facility with which cholesterol is removed from the peripheral blood. An increased rate of removal may then result in an increased elimination through the bile or deposit in the tissues or both as is seen in pernicious anemia.

Future work on this obscure problem may lie in a correlation of the cholesterol level of the blood to the functional state of the reticulo-endothelial system in various diseases, the relation of cholesterol to growth of cells and to the concentration of the serum proteins, as well as the influence of the physico-chemical condition of the medium and the colloidal state of cholesterol itself.

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THE CARDIAC OUTPUT OF MAN[1]

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"Meanwhile I know and state to all that the blood is transmitted sometimes in a larger amount, other times in a smaller, and that the blood circulates sometimes rapidly, sometimes slowly, according to temperament, age, external or internal causes, normal or abnormal factors, sleep, rest, food, exercise, mental condition and such like." This sentence published over three hundred years ago by Harvey states the problem of the cardiac output and gives qualitatively the main factors which influence the circulation of man. Today, we have not completely solved this problem in a quantitative way, but in the last few years great advances have been made. It is a small part of this story of the cardiac output of man that I wish to relate tonight. For addressing you on this topic, I feel sufficient warrant in the fact that what I shall have to say attempts to advance in a small way the work begun by the illustrious one after whom this Society is named.

It has not been due to a lack of effort on the part of a long line of investigators of the first rank that the work begun by Harvey has progressed so slowly, but rather to certain intrinsic difficulties attendant upon the measurement of the output of the heart of the human subject.

We can disregard for our present problem the numerous studies which have been made in the past hundred years of the cardiac output of perfused hearts, heart-lung preparations, and anesthetized and operated animals; for the reason that experiments of this type, although very valuable in advancing our knowledge of the physiology of the heart by showing what it can do under certain controlled conditions, tell us nothing about its output in the normal animal or man. There are, however, three general types of methods which have been used in an attempt to solve the problem of the cardiac output in normal animals or man, *viz.*: (*a*) methods based on the Fick principle—direct or indirect, (*b*) methods based on the rate of absorption through the lungs of some foreign gas, (*c*) measurements by means of x-rays of the systolic and diastolic shadows of the heart.[2] Since the widely divergent results in this field have been due largely to difficulties and inaccuracies in many of the methods used for estimating cardiac output, it is essential that we consider for a few moments technical details, and give the evidence for the reliability of the method with which most of the results to be discussed have been obtained.

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Over half a century ago, Fick (15) announced the principle upon which many methods have been based. As is well known, this consists in determining the total quantities of oxygen or carbon dioxide in samples of blood taken from the left and right ventricles, and simultaneously estimating the quantity of oxygen absorbed or carbon dioxide given off by the animal through the lungs. If we do not consider the now discredited view held by Bohr and others that the lungs are the seat of a considerable oxidation, the theory of the method would appear unimpeachable. Technical difficulties have, however, prevented its very wide application, and frequently detract from its accuracy.

The classical investigation by this Fick method is that of Zuntz and Hagemann (60) on the horse during rest and work. This was done without anesthesia and with only the slight operations which were necessary to introduce a sound into the jugular vein and to cannulate an artery. The important finding that the cardiac output is greatly increased in muscular work over rest was the result of this research. Some years later Barcroft and his coworkers (3) succeeded in carrying out experiments on normal unanesthetized, unoperated goats. They determined the oxygen consumption by the use of a special mask and obtained arterial and mixed venous blood by puncture of the left and right ventricle with a syringe and needle.

Using slight modifications of the above method, it has been possible to study the cardiac output of a series of dogs over a period of two years (42, 43). Since this method is a much more direct one than the various methods which have been used on the human subject, a brief presentation of these results may be of interest. Of the five dogs studied two have shown a fairly constant figure for the cardiac output under resting conditions, while the three others have shown much more variation. It is important to note that the first two animals were males, the last three females, one pregnant. The most important findings of this study would appear, however, to be the demonstration that the minute volume of the circulation is uninfluenced by changes in pulse rate which occur spontaneously or which are produced by the use of atropine, and the variability of the output of the heart per beat.

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[2] A fourth principle which had been previously used only in animal experiments has recently been tried on the human subject (50a). This is an injection method, in which a foreign substance is introduced into the venous blood and the cardiac output calculated from its concentration in the arterial blood.

The application of this Fick principle has been one of the classic lines of attack on the problem of determining the cardiac output of man, but the simplicity and directness of the method as used on animals, have been lost due to the fact that mixed venous blood cannot be obtained and some indirect means of estimating its gaseous contents must be used. The oxygen or carbon dioxide content of the blood of the left ventricle can be easily obtained from a sample of blood drawn by arterial puncture or indirectly from the tension of these gases in the alveolar air and the dissociation curve of the subject. Various devices have been used in determining the gas tensions in the venous blood, but they are all based on the principle of using the lungs as an aerotonometer. The pioneer work of Loewy and v. Schrotter (40), Plesch (52), and especially Douglas and Haldane (11) laid down the principles for the later development of methods of this type.

The second type of method based on the study of the rate of absorption through the lungs of some foreign gas originated with the attempt of Bornstein (6) to measure the rate of elimination of nitrogen from the body when pure oxygen is breathed. In attempting to use Bornstein's method Krogh and Lindhard (33) were unable to satisfy themselves of its accuracy or practicability and devised their well-known nitrous oxide method based upon the same general principle. A reinvestigation of the use of nitrogen for determining the cardiac output has recently been made by Marshall, Harrop and Grollman (45) and the difficulty and impracticability of the method demonstrated even when the original errors have been eliminated. Since it is along this line that a modification of the Krogh-Lindhard procedure which we believe to be both extremely simple and accurate has been made, we shall return to its discussion in a moment.

As regards the third general type of method, the use of the x-ray shadows of the heart, I can say nothing having had no personal experience with it. Meek and Eyster (48) at Wisconsin have been mainly instrumental in its development and if put upon a practical basis it should prove a very valuable aid to gasometric methods as an independent check upon their accuracy and for use in the many physiological and pathological conditions where gasometric methods fail.

The method of determining the cardiac output which has been devised in our laboratory and used in the investigations about which I shall speak, is based on a measurement of the rate at which a foreign gas is absorbed during the passage of blood through the lungs. Various foreign gases have been tried and several of them used in this method—ethylene, nitrous oxide and acetylene. The use of acetylene as proposed by my associate Grollman would appear to render the whole procedure extremely simple and of a high degree of accuracy. As now used in our laboratory the method may be described as follows. The subject after a period of rest or exposure to some special condition under which the determination is to be made, has his oxygen consumption determined by one of the usual methods. He then rebreathes from a rubber bag, containing a mixture of acetylene, oxygen and air, for a period sufficiently long to bring about mixture in the lung-bag system (15 to 18 seconds) and a sample is taken in an evacuated tube. After 5 seconds more another sample is taken. An analysis of these two samples, the barometric pressure, and the oxygen consumption give all the data necessary for calculating the output of the right ventricle and hence also of the left ventricle. For the technical details and method of calculation the original papers already published must be consulted (44, 20).

You may well inquire concerning our evidence regarding the accuracy and trustworthiness of this or any other method for determining the output of the human heart. Since the determination of the cardiac output in man with any high degree of accuracy and simplicity has been the crux of the whole problem for many years, we must consider the evidence in some detail. In the first place, it may

TABLE 1

Values of cardiac output by different methods

PRINCIPLE	METHOD	OBSERVER	NUMBER OF SUBJECTS	POSITION	CARDIAC OUTPUT		
					Range	Average	Average per square meter
					liters per minute	*liters per minute*	*liters per minute*
Foreign gas, N_2O	Krogh-Lindhard (33)	Liljestrand and Stenström (37)	10	Recumbent	3.0–4.6	3.89	2.40
Foreign gas, N_2O, C_2H_4	Marshall-Grollman (44)	Marshall and Grollman (44)	16	Sitting	3.1–5.8	4.78	2.62
Foreign gas, C_2H_2	Marshall-Grollman (44)	Grollman (24)	50	Sitting	2.7–4.7	3.88	2.21
Fick, O_2	Burwell-Robinson (7)	Burwell and Robinson (7)	11	Sitting	3.5–6.8	4.65	2.56
Fick, O_2	Eppinger-Papp-Schwarz (13)	Eppinger, Papp and Schwarz (12)	14		2.6–7.5	4.23	
Fick, O_2	Redfield-Bock-Meakins (53)	Hayasaka (27)	7	Recumbent	2.8–3.9	3.38	2.22
Fick, O_2	Redfield-Bock-Meakins (53)	Grollman (25)	10	Sitting	2.9–5.2	3.71	2.21*
Fick, CO_2	Field-Bock-Gildea-Lathrop (17)	Lawrence, Hurxthal and Bock (34)	10	Recumbent	4.3–8.9	6.80	3.75†
Fick, CO_2	Field-Bock-Gildea-Lathrop (17)	Lawrence, Hurxthal and Bock (34)	10	Sitting	4.3–7.1	5.76	3.18

* Grollman has also on this same series of subjects estimated the cardiac output by the acetylene method and finds excellent agreement between the two methods in each individual subject. The average for the values obtained by the use of acetylene was 2.13 liters per square meter, as opposed to 2.21 by the Fick method.

† Field, Bock, Gildea and Lathrop (17) also report results by this method on 19 individuals in the lying position which average 3.73 liters per square meter; Field and Bock (16), on 10 individuals lying 8.18, sitting 5.94, but give no data for calculating surface area; Turner (57), on 25 individuals lying, 3.89 and sitting, 3.47 liters per square meter body surface.

be said that the underlying assumptions upon which our method depends have been critically examined and their validity experimentally demonstrated.[3] In the second place, duplicate determinations made on the same subject under identical conditions always agree closely. In the third place, determinations on a series of subjects using in one case ethylene, in another nitrous oxide, and in still a third acetylene agree within the experimental analytical errors. Lastly, and probably most important is the fact that several methods based upon different principles give results which are of the same order of magnitude as those obtained by our method. From what we now know about the behavior of the cardiac output under different conditions, it is clear that in comparing results obtained by different methods, the conditions under which the determinations have been made should be identical. This has been very rarely realized, as it is now known that "standard conditions" for estimating the basal cardiac output must be more rigid than those used for basal metabolic rate determinations, but it is also now clear that in a series of determinations on different individuals in the so-called "basal condition," the average obtained will not be more than a fraction of a liter higher than that obtained under rigid standard conditions. In table 1, I have accordingly collected all determinations which have been made by any method in the basal condition on a series of subjects sufficiently large to average out the errors of the method.

It is seen that the average values for the cardiac output in the basal condition obtained by all the different methods with the exception of the last, vary only from 2.2 to 2.6 liters per square meter of body surface. The extremes (2.2 and 2.6) were obtained in our laboratory on different series of subjects by the same method and are undoubtedly to be explained by the fact that in one case the subjects were taken in the ordinary basal condition, while in the case of the lower values more rigid standard conditions were imposed. The higher results obtained by the carbon dioxide Fick method of Bock and his collaborators need comment. With some subjects the results obtained by this method agree perfectly with those by other methods, but with others the results are distinctly higher.[4] No obvious fault can be seen in the underlying assumptions of the method, but the facts that duplicate determinations may differ rather widely, that this method frequently gives a much higher output when lying than sitting or standing, and that it gives higher results than those of any other method, would lead one to question its accuracy.

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[3] It might appear at first hand that the most satisfactory evidence for the accuracy of any method would be established by checking it in animals against the direct Fick procedure. However, three methods, the nitrous oxide (59), the ethyl iodide (29), and the injection procedure of Moore et al. (50a), which have been found to agree with the direct Fick procedure on dogs, all appear to give different results when used on man. An experience some years ago of checking exactly a nitrogen method on dogs with the Fick and later finding the method unquestionably inaccurate for man makes me believe that such checking on animals is less satisfactory evidence of accuracy for man than that obtained in other ways.

Many determinations are reported by the ethyl iodide method of Henderson and Haggard (28), but I can find no series which has been carried out under strictly basal conditions. The results obtained, however, are as high or higher than those of the Bock method (e.g., under nearly basal conditions Cullis, Rendel and Dahl (10) find in 12 subjects 5.1 to 10.4 liters with an average of 7.5, and Mobitz (49) in 11 individuals finds an average of 8.97 or 4.93 liters per square meter of body surface).[5] Many investigators (29, 35, 50, 54, 58) have, however, disproven the validity of the assumptions involved in the ethyl iodide method as originally proposed, and in fact Starr and Gamble (55), using what appears to be an accurate modification of the ethyl iodide procedure, have obtained on two subjects in the basal condition results (2.22 and 1.95 liters per square meter of body surface) which agree perfectly with those of other methods. Therefore, we may consider it practically certain that methods are available for obtaining essentially correct values for the cardiac output of man.

Despite the fact that the average values given on a series of subjects by several methods agree perfectly, it is quite certain that not all of these methods are of equal accuracy in individual determinations. Many of them give varying duplicate values where it is certain no change is taking place in the circulation, so that, a general conclusion, obtained by their use, may be true more in a qualitative than a quantitative way.

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[4] Comparisons of two different methods have occasionally been made but only on 1 or 2 subjects. The fallacy of drawing conclusions from so few subjects is well illustrated by the work which has been done in the comparison of this method with others.

[5] Kaup and Grosse (32) in a recent publication state that with a modification of this method they no longer obtain high results for the normal cardiac output. On 16 individuals at rest, they state that the average by the ethyliodide method is 4.81, and by the Krogh-Lindhard nitrous oxide method, 4.78 liters.

The first question of prime importance is what is the value for the cardiac output of normal man at rest under standard conditions which can be easily reproduced. It would seem obvious that a large individual and a small individual will not have the same cardiac output unless the factor of size is taken into account, but most investigators have been unable to find any relation to weight, surface area, vital capacity or other measurements. Rather wide limits have hence been given for the normal values of the circulatory minute volume. This variability of the normal would now seem to be more apparent than real and due mainly to two causes; firstly, the inaccuracy of many of the methods used and secondly, the fact that "standard conditions" for determining the basal cardiac output must be much more rigorous than those used for estimating the basal metabolism. Thus psychic influences, previous physical exercise, and external temperature changes which may have little influence on basal metabolism will decidedly affect the cardiac output of many individuals. A long tedious street car ride to the laboratory even if a long rest period is used afterwards may result in an elevated value for this function (24).

Burwell and Robinson (7) found the cardiac output per square meter of body surface to be 1.9 to 2.5 liters in 8 of their 11 subjects, the other 3 showing higher values. Hayasaka (27) in his 7 normal subjects found 1.9 to 2.6 liters per square meter as the cardiac output. Grollman (24) in our laboratory examined 50 young adults in the third decade of life under "standard conditions" and found the circulatory minute volume to be 2.2 ±0.3 liters per square meter of body surface or about as constant as the basal metabolism. This is an extremely important contribution as, when extended to include other age groups, it will permit us to predict the basal cardiac output of any individual as accurately as is now done for basal metabolism, and to find slight deviations in disease which have been previously impossible to determine with any certainty.

As this series of 50 normal individuals is by far the largest reported under standard conditions and as I believe the standard conditions to have been most satisfactory for determining the basal value of the cardiac output, I give a summary of this work in table 2.

This table then gives what we may call the normal values for the basal cardiac output for young adults. It is seen that the arterio-venous oxygen difference is the most constant and the cardiac output per unit of body surface the next in order of constancy. One cannot use, however, the arterio-venous oxygen difference as a measure of the normalcy of the heart output, because under many conditions it is found that this may remain constant with a changing or changed cardiac output, or may be increased with an unchanged output. It would appear best to relate the cardiac output to surface area and to calculate the expected normal in the same way as is commonly done for basal metabolism.

TABLE 2

Basal cardiac output of 50 normal young adults

	ARTERIO-VENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT PER SQUARE METER BODY SURFACE	CARDIAC OUTPUT PER KILOGRAM BODY WEIGHT	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER KILOGRAM
	cc. per liter	*liters per minute*	*cc. per minute*	*cc.*	*cc.*
Range	55–67	1.90–2.49	50–75	38–84	0.67–1.22
Average	59	2.21	60	62	0.95
Average Deviation from Mean	2.6	0.14	4.6	7.1	0.11
Average Percentage Deviation from Mean	4.4	6.4	7.7	11.5	11.6

From what has been said regarding the constancy of the basal cardiac output per square meter of body surface of different individuals, it is clear that this function must also be constant for any given individual at different times. In spite of the fact that many results have been reported of the variability of the heart output in some individuals when determined on different days and although we ourselves have reported this finding, it appears now that this variability is due to the fact that the conditions under which the estimation is made are not sufficiently controlled to obtain a true basal value. The lowest value found in such a varying series of determinations will be found to be the true basal value. As direct evidence in this regard, I may say that my associate, Grollman, has now followed the cardiac output of two individuals for a period of over a year and finds that when taken under rigidly controlled standard conditions, it is quite constant in both. One of these individuals was previously reported as having a varying output on different days. Thus, his basal output is 3.9 ±0.2 liters, but it can rise to 4.5 liters if the standard conditions are not rigidly maintained.

Since it has been shown that the basal metabolism of different mammals is the same per unit of surface area, it is interesting to inquire whether the same is true of the basal cardiac output of different animals. Table 3 includes the data that can be collected for unanesthetized animals of different species. The average cardiac output per square meter of body surface (calculated from Meeh's formula), the cardiac output per 100 cc. of oxygen used, the basal metabolism taken from Voit's table, and the average metabolism found during the cardiac output determinations are given.

TABLE 3

Cardiac output of different animals

ANIMAL	CARDIAC OUTPUT		BASAL METABOLISM	OBSERVED METABOLISM	OBSERVER
	Per square meter	Per 100 cc. oxygen used			
	liters per minute	*liters per minute*	*calories per 24 hours*	*calories per 24 hours*	
Man	2.62	2.02	1,042	902	Marshall and Grollman (44)
Dog	2.86	2.02	1,039	983	Marshall (43)
Goat	3.07*	1.77		1,200	Barcroft et al. (3)
Rabbit	1.69	1.33	776	880	Odaira (51)
Horse	5.84	1.46	948	2,700	Zuntz and Hagemann (59)

* Surface area calculated from constant 0.115, between sheep and calf.

It is seen that with the exception of that of the horse, the values per square meter of body surface are of the same order of magnitude. During the experiments the horse's metabolism was almost 300 per cent above the basal which explains the abnormal value. Considering the many errors which may be present to vitiate results in attempting to make such a comparison as the above, it would seem that the basal cardiac output per square meter of body surface may be almost as constant for different mammals as is claimed for the basal metabolism.

A remarkable supposed effect of posture on the cardiac output has been claimed by several observers, some finding that the heart may pump twice as much blood when the subject is recumbent as when he is in the erect position. Lindhard (38) first announced this effect of posture, but limited its operation to female subjects, males being unaffected. Collett and Liljestrand (9) apparently confirmed the effect in the case of 1 female subject, but a careful examination of the variability of duplicate determinations in these two papers, as well as the fact that subsequent investigators using the same heart output method find very low values for the recumbent position makes one hesitate to accept the finding. Recently extensive work has been carried out on the effect of posture. Observers (16, 34, 57), using the carbon dioxide method of Bock and his associates, find in general a marked influence which appears to be confirmed by the results obtained with the ethyl iodide method. The latter method, however, cannot be used as evidence, and, indeed, Starr and Gamble (55) with their modification of it find such low values for the lying position that it is difficult to conceive of them decreasing for other positions.

A reinvestigation (19) of the posture question in our laboratory, by the method of Marshall and Grollman, has presented strong evidence that the effect does not exist or is quite negligible. On 10 subjects the average values for the cardiac output were, recumbent, 3.83; sitting, 3.65; standing, 3.62 liters per minute. This has now been further confirmed (25) by using two entirely different methods on 4 subjects. The acetylene method gives as averages for the lying position 3.72, for the sitting 3.44, and for the standing 3.33; while the triple extrapolation method (53) based on the Fick principle gives lying 3.67, sitting 3.60, and standing 3.72 liters. A glance at table 1 also confirms this general conclusion, for it is seen that the averages of different methods agree (with the exception of that of Bock) with each other, independent of whether or not the subjects have been examined in the recumbent or sitting position. One may take it as established, therefore, that the position of the subject is without influence on the cardiac output.

Two important conclusions, however, are implied in this constancy of the heart output with change of position. In the first place, as is well known, the pulse rate is considerably higher in the standing than in the recumbent position, so that the systolic output varies with the position of the subject. Secondly, the oxygen consumption is much greater in the standing position, so that the arterio-venous oxygen difference and hence the oxygen utilization rises from its value in the sitting or lying posture.

Ever since the time of Lavoisier, it has been known that the ingestion of food results in an increased oxygen usage by the body, and a great deal of knowledge about this effect has been obtained. As regards the cardiac output, however, very few studies of the influence of food have been made. Previous studies (9, 13, 31), due to large accidental errors in the methods employed have only demonstrated the fact that the ingestion of food increases the heart output. Recent studies (22) in our laboratory, however, with the very accurate acetylene method give us clear information concerning the time relations of the effect of the ingestion of varying amount of food. Figure 1 illustrates the main findings. It is seen that there occurs a very prompt rise in the cardiac output, which may remain at this high and practically constant level for 1 to 3 hours depending on the size of the ingested meal. The return to the normal basal value is much quicker in the case of a light meal than a heavy one, the latter frequently

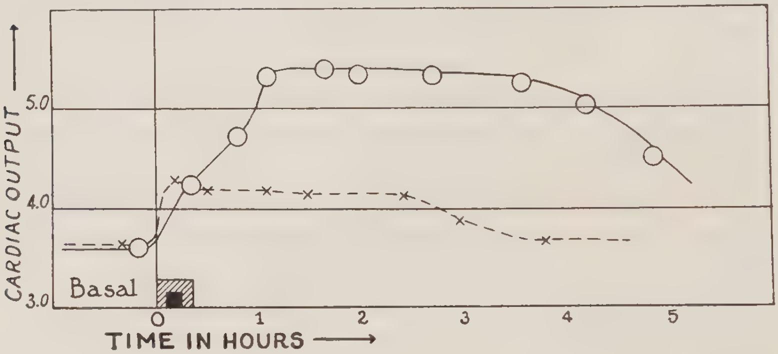

Fig. 1. Effect of Ingestion of Food on the Cardiac Output

The broken line represents the cardiac output after ingestion of a very light meal and the solid line after ingestion of a very heavy meal. The solid black rectangle represents the time taken in ingesting the light meal and the light rectangle in the ingestion of the heavy meal.

showing its effect 7 hours later. Even the ingestion of large quantities of fluids (water and salt solution) may increase the cardiac output, the rise usually being around 10 per cent, but occasionally as much as 50 per cent above the basal value (21, 31).

It is well known that the circulation in the skin varies with the temperature of its surroundings. It is not clear, however, whether this change in circulation is brought about by a change of cardiac output, by a redistribution of blood in the body, or by both. Lindhard (39) studied the effect of hot and cold baths and found an increase in cardiac output in three out of four subjects exposed to 41° to 42°C., and in two out of four subjects a decrease when put in a bath at 15° to 17°. Barcroft and Marshall (4) in one of the two subjects studied, found a constant increase on exposure to warmth, and also an increase in circulation with exposure to cold which just produced shivering. Although the general conclusions of these observers would appear to be correct, the errors incident in their methods and the lack of properly controlled conditions for their experiments make it advisable to repeat and extend this work. From work now in progress we can definitely say that exposure to cold not sufficient to produce shivering decreases and exposure to heat increases the cardiac output. However, since we might expect this response to external temperature to be subject to more individual variation than some of the other effects which have been discussed, more subjects must be studied over a wide temperature range before final quantitative conclusions can be drawn.

Another factor which may change the cardiac output and which has been emphasized (9, 13) without completely satisfactory evidence in the past, is the emotional state of the subject. It is well known to all of you that marked rises in pulse rate and blood pressure can be caused by psychic disturbances, but it is less clear as to whether these changes are of vasomotor or cardiac origin. Some experiments (23) recently carried out in our laboratory have clearly shown that the rise of blood pressure is partly at least cardiac in origin or in other words that psychic disturbances may cause an increase in the cardiac output. In the series of individuals studied, however, it was found that the pulse rate and blood pressure always showed concomitant increases; mild disturbances which do not affect these cause no change in the circulation rate. These results emphasize the importance of avoiding psychic disturbances when the basal cardiac output is being determined, and also indicate that by following the blood pressure and pulse rate information can be obtained as to whether or not the true basal cardiac output is being estimated.

Turning now to a discussion of the cardiac output during muscular exercise, I find that a survey of the literature on the subject leaves me with a feeling that much more work must be done before many of the conclusions which have been drawn can be finally accepted. That the heart pumps more blood during muscular work than when the organism is at rest was definitely decided, as you well know, at the end of last century by the experiments of Zuntz and Hagemann (60) on the horse. Other important questions, such as the extent to which the systolic output can rise over its basal value, the proportionality of the circulatory minute volume to the oxygen consumption, the effect of training, the difference in cardiac output with different types of work of the same severity as judged by oxygen consumption cannot be answered with certainty at present. Aside from the fact that large errors are inherent in many of the methods used in the past, it is by no means certain and, in fact, very improbable that most methods can be used with any accuracy at all except in very mild exercise. This is a technical but inherent difficulty due to the markedly increased circulation rate and applies to our own method. That the systolic output is increased during exercise is implied in the acceptance of the low values herein given for its basal value; by no other means could the amount of oxygen known to be absorbed at the lungs during exercise be transported to the tissues. Indeed in dogs, I found that the light muscular exercise involved in shivering may cause the systolic output to be doubled (43). In man, it is certain that the systolic output can vary: change of posture, ingestion of food, variation of external temperature, administration of atropine and many other factors can change the output per beat. Several investigators (5, 39, 46) have concluded that during exercise the cardiac output varies directly with the oxygen consumption, the utilization, therefore, being constant. However, in the normal unanesthetized dog, changes of 30 per cent or more may occur in the oxygen usage with no change in the circulation rate. This, together with the fact that the metabolism may rise markedly on standing, which may be considered very light exercise, over its sitting level with no change in heart output, makes me think that in very mild exercise the increased oxygen may be supplied to the tissues more by an increase in utilization than by an increase in heart output.

The necessity of having an extremely accurate method for estimating the cardiac output of man and of rigidly controlling the conditions under which the determination is made is well shown in determining the changes which occur at high altitudes or under diminished oxygen pressure. It seems quite reasonable to suppose that the circulation should participate in the many compensations in the body which take place at high altitudes, but previous investigators (2) have not found such expected changes in the cardiac output. This past summer, Grollman from my laboratory went on an expedition to Pike's Peak, Colorado, for the purpose of studying the heart output under these conditions with the very accurate acetylene method. The results show clearly that the basal cardiac output is increased during the first days of residence on the Peak, but soon returns to normal. The maximum increase found was about 40 per cent. Subsequent experiments (25) in the laboratory have shown that the breathing of low oxygen mixtures does not produce an immediate increase in cardiac output until the inspired oxygen is decreased to about 11 per cent.

At this point, I cannot resist saying a few words about the problem of the regulation of the cardiac output of the human subject concerning which, however, our knowledge is meager. Such knowledge as we possess has been obtained chiefly from acute experiments on animals. That we cannot transfer bodily to man results and conclusions obtained by such experiments on the regulation of the circulation of animals, especially if these have been anesthetized and operated upon or converted into "pieces of animals" for better control of variables, seems to me to be certain beyond question. Nevertheless, just this is being more or less unconsciously done every day. As Haldane has so ably maintained, if we wish to learn about human physiology, we must experiment on the human subject.

That the regulation of the heart and circulation is a double regulation—nervous and chemical—similar to that of most systems and organs in the body seems certain. However, we know very little about the chemical regulation and the very extensive and detailed data concerning the nervous regulation have practically all been obtained on operated and anesthetized animals. The difficulty and danger of this transfer without reserve of the conclusions obtained from such data to normal animals or man may be best illustrated by giving concrete examples. As has been earlier stated, in the normal unanesthetized dog at rest, changes in pulse rate of 100 per cent or more produce no change in the circulatory minute volume of the heart (42, 43), while if the same type of experiment is repeated on the urethanized and operated animal, the usual effect of changes in pulse rate is found to be corresponding changes in the minute output of the heart (56). Another example is the finding of Cannon and Lewis (8) that in unanesthetized cats, "with accelerator influence alone active, the heart rate varies greatly as they change from rest and calm to activity and excitement. In such animals anesthesia increases the rate to a point below the maximal and there fixes it, so that reflex and direct stimulations have little or no influence." Many more examples could be given not only in the circulatory field, but in other parts of the wide realm of Physiology.

We know now with certainty that ingestion of food, changes of external temperature, psychic disturbances, lowered oxygen tension in the inspired air, and muscular exercise do all change the cardiac output, but we are at present far from understanding the mechanism by which these changes are brought about. It is, of course, obvious that the output of the heart cannot exceed its input, hence where the cardiac output is increased the input must be also increased. But whether this increased venous return to the heart is brought about primarily by changes in the cardiac mechanism, by alterations in the blood vessels, or by both cannot be determined with certainty at present.

As regards the nervous factor in the regulation of the heart, it is easy to see how the inhibitory and accelerator nerves can, by increasing pulse rate, act during exercise, when as large a pumping capacity per minute as possible is demanded, but it is also certain that changes in heart rate need not be accompanied by any change in the minute volume of blood expelled. To say, as is done in most text books, that the pulse rate changes are in accord with Marey's Law to keep the mean arterial blood pressure constant, is obviously useless when one is dealing with the normal unanesthetized animal or man, where such pulse rate changes cannot influence the mean arterial pressure. However, in many conditions the cardiac output per minute is so regulated as to keep the arterial blood pressure fairly constant. Thus when vasodilatation or vasoconstriction of peripheral vessels is brought about by changes of external temperature, the cardiac output increases or decreases so that the arterial pressure is not changed. The experiments of Gaisböck and Jarisch (19) show that after administration of sodium nitrite the heart output is increased and the blood pressure unchanged. These same observers (30) studying the mechanism by which the increased circulation in exercise is produced, found that no lowering of blood pressure resulted from the hyperemia following anemia of several extremities, but a marked increase of cardiac output. From what has been said, it is obvious that the systolic output frequently varies inversely as the pulse rate but regarding the mechanism of this change in strength of heart beat there is no clue. One might think at once that this is solely an operation of Starling's "Law of the Heart"—that the strength of beat is proportional to the diastolic size, but the diastolic size may remain unchanged while the pulse rate increases from 55 to 110 per minute (47). This fact taken together with certain findings on the diastolic size of the heart during and after exercise (41) brings up the question as to whether or not the "Law of the Heart" is a law at all for normal animals or man.

In regard to the chemical control of the circulation, when we have recalled the stimulating action of adrenaline (14) on cardiac output there is little more that is certain to add. It is true that several authors (5, 11) have attempted to show that the circulation is regulated by the hydrogen ion content of the arterial blood, just as the respiration is, or rather as it was supposed to be. But such evidence as exists for this view has been obtained on morphinized (26) and anesthetized animals (12) and does not agree with observations made on the normal unanesthetized dog (42) or man (36, 39).

Should some of you still feel that I have overemphasized experiments on the normal unanesthetized animal or human subject, where many claim that the variables are too numerous for a good experiment, to the exclusion of animal experiments where conditions are controlled at the expense of anesthetics and operative procedures, I can only recall for you again the dangers of transferring conclusions obtained in this latter type of experimentation to the normal animal or human being. It is remarkable that so much of this has been done in spite of the fact that over 30 years ago Pavlov taught us how misleading this type of experiment could be in regard to the digestive glands, and in spite of the warning contained in the writings of Haldane in England and Yandell Henderson in this country in this regard.

You might naturally expect me before this audience at least to touch upon the important problems of the changes in cardiac output brought about by disease. However, it appears at present impossible to say very much along this line which would stand the test of time. A considerable amount of literature exists upon this subject, but a perusal of it leaves one with the feeling that the time is not yet ripe for many definite conclusions. The most suggestive data have been obtained in cases of hyperthyroidism, fever, hypertension and anemia. The main difficulties would appear to be the use in the past of methods with large accidental errors, the lack of proper attention to maintaining standard conditions for the determinations, and the lack of repeated determinations on the same subject throughout the course of a disease. Another point which I cannot refrain from advancing in the nature of a warning is the fact that the validity of the fundamental assumptions underlying any method now used for determining the cardiac output of man must be carefully scrutinized in every new type of case where one changes from working on the normal to the abnormal individual. In many cases much tedious work along the same lines which have been pursued in developing a method for the normal subject, must be carried out before the trustworthiness and accuracy of the method can be gauged for the pathological subject. The careful investigation with all necessary controls of a single pathological condition will carry much more weight with careful critics than the publication of large masses of statistical data concerning many different diseases. This situation is unfortunate, but I see no escape until we have learned more about the use of the newer heart methods in studying disease, if we are to build firmly upon the foundation which Harvey left us.

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THE ERYTHROCYTE IN MAN[1]

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I. THE ERYTHROCYTE

1. FUNCTION AND NATURE OF THE ERYTHROCYTE

The essential chemical nature of life is a process of combustion involving the continuous building up and breaking down of tissue. For this chemical process there is needed a constant supply of oxygen and simultaneous removal of carbon dioxide. Blood plasma is capable of holding only a small quantity of these gases, a quantity which is, however, quite sufficient in some cold-blooded animals. In the mammal, on the other hand, a more efficient means of gaseous transportation is necessary. This function is performed by hemoglobin, which, through its special properties has made possible life on a scale higher than that of cold-blooded animals.

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A simple solution of hemoglobin in the concentration in which it is found in the blood, would, however, as Barcroft pointed out (7), have certain physical properties which would make its occurrence in the circulating fluid extremely deleterious to the organism. It would have an osmotic pressure of more than 100 millimeters; it would add materially to the viscosity of the blood; it would tend to stagnate along the capillary walls and possibly diffuse out into the tissue spaces. The enclosure of hemoglobin in special cells, capable of efficiently transporting it, readily overcomes these disadvantages.

The erythrocyte in man and in all the other mammalia with the exception of the group Camelidae, is an extremely small, biconcave, disc-like body. Hartridge (92) has pointed out that the unusual shape of the red cell has certain physiological advantages. Thus, the surface exposed is larger for a given bulk. Gough (70) has calculated that in the corpuscle no point in the interior is distant more than 0.85μ from the surface, whereas, if it were spherical, not only would the center be 2.5μ from the surface, but the surface of the corpuscle would be 20 per cent smaller. Again, the form of the red cells is such as to allow the contents to become saturated in all parts of the corpuscle at the same time. If the cells were flat discs of uniform thickness, the peripheral parts would become saturated earlier than the central portion. As a result of the biconcave shape penetration is uniform.

Water (about 61 per cent) and hemoglobin (about 36 per cent) make up the main bulk of the red blood corpuscle. Small quantities of phosphatides, cholesterol, glucose, urea, creatinine, uric acid, glutathione, thioneine, adenine-ribose-nucleotide and various inorganic ions including potassium, chloride, magnesium and phosphate make up a little more than 2 per cent of the corpuscle (26). Of the metals, iron is the well-known constituent of hemoglobin. Copper, according to Elvejhem (54), is present in the red cell but not in the hemoglobin portion. Cameron (26) has calculated that the red corpuscle contains approximately one million million molecules.

Since the early days of microscopy, opinion has fluctuated regarding the fluid or solid nature of the red corpuscle. Schwann, Schafer, and many other physiologists have strongly maintained that the red cell is composed of a membrane containing a fluid or semifluid substance. Schafer (182) bases his conclusions on the following premises: (1) in hypotonic solutions red cells assume a globular form, whereas a solid body imbibing water would, in swelling, retain its former shape; (2) as the corpuscles circulate in the capillaries slight variations of pressure cause distortion, which would be impossible if they were solid; (3) in the corpuscles of ovipara the nucleus readily becomes displaced.

Gough (70) offers another premise for such a conclusion, namely, that hemoglobin crystals separate freely in the interior of a corpuscle. He considers the contents to form a hydrophile (i.e. emulsoid) colloid system, and the surface film to contain lipoids in a solid state, as is shown by the microscopic appearance of "ghosts," and by "the agglutinating action of polyvalent kations in extremely dilute solutions."

The great stumbling block which has prevented the acceptance of the fluid hypothesis is that stated by Hewson (99) and Rollett (174), "How can one imagine that a bladder with a flexible membrane and floating in a liquid should assume a discoid shape?" Of importance in this connection are the observations of Rice (172) who found that the particles of a lecithin emulsion in water assume the same form as mammalian red cells, being circular discs which are dumbbell-shaped in cross-section, and varying in diameter from 5 to 10μ. These findings suggest that red corpuscles are rather inert bodies whose form and dimensions depend upon the physical forces at work in the medium in which they are suspended (55). Thus, according to Gough (70), the shape of the red cell is the result of two sets of forces: (*a*) tension of liquid surfaces tending to cause a spherical shape; (*b*) repulsive forces between the dispersed particles of the corpuscular contents which tend to cause the flat shape.

Geometrical considerations lead Ponder (157) to conclude that the red cell is a balloon-like body with a membrane and a liquid content. It is rather generally believed that the "surface membrane" is made up of lipoid substances. Experiments on the electrokinetic properties of red blood cell suspensions, however, lead Oliver and Barnard (144) to believe that the red corpuscle possesses a surface of globulin.

2. THE SIZE OF THE ERYTHROCYTE

It is possible by various methods to determine the diameter, volume, and thickness of the red corpuscle. These methods will first be briefly discussed and normal values given.

a. Diameter of the erythrocyte

Methods of measurement. Price-Jones (161) uses blood smears, dried in the air and fixed and stained in Jenner stain for two minutes and in a weak aqueous solution of eosin for another two minutes. The image of the microscope field is projected on to a sheet of paper the magnification of the cell image being known. A thin portion of the film having been chosen, the red cells are outlined in pencil and two diameters (maximum and minimum) measured, the mean of these being accepted as the diameter of the cell. Price-Jones measures 500 cells in this way. Ponder and Millar (159) measure diameter by photographing, under suitable optical conditions, cells in plasma and measuring from the negative.

Both of these methods are obviously very laborious. They have the merit of relatively great accuracy. Frequency curves of the occurrence of red cells of various sizes can be plotted and an accurate and valuable conception of the degree and extent of variation in size can then be derived.

An ocular micrometer which can be placed into the eyepiece of any microscope has been devised and is very popular. This micrometer can be calibrated by means of a slide micrometer for the particular tube length and lenses employed. The cells in the thin portion of a blood smear, stained in the usual manner, are measured by simply bringing them under the scale of the micrometer ocular. Two diameters (maximum and minimum) of all cells coming under the scale can be measured or, as is more often done, one diameter of all round cells appearing under the scale, is measured. This method is very simple and readily available. Accuracy, however, is sacrificed for simplicity.

Diffraction methods, first discovered by Thomas Young in 1823, have recently been employed for the measurement of the diameter of erythrocytes by Pijper (151) (diffraction micrometer), Millar (134), Emmons (56) (eriometer), and Eve (58) (halometer). These methods are based on the principle that when a beam of white light is sent through a blood smear it is broken up (diffracted) by the blood cells into the spectral colors. From the distribution of the colors the mean diameter, the degree and quality of anisocytosis, and the degree of poikilocytosis of the red cells can be determined. The mean diameter of a large number of cells (a million) is determined and also the mean diameter of both the largest and smallest cells which are present in the smear in considerable number are given. Pijper (151) says, "The application of the method is simpler than the description," and requires no more time than the estimation of hemoglobin. However, these methods only measure the size of the corpuscles in mass and give average figures only. Variability cannot be accurately determined. They are very convenient for quickly finding the mean diameter and are useful in following changes in average diameter in the same patient.

Normal cell diameter. There is some variation in normal average cell diameter as reported by different investigators. This is probably largely due to differences in the technic employed. Price-Jones (161, 163) found in 100 healthy adults a mean diameter of 7.20μ. He concluded that the normal range of mean diameter is 6.69μ to 7.72μ. The variation in the size of the cells, as expressed by their coefficient of variation, was 5.2 per cent. The extremes in size noted in the 100 presumably healthy individuals were 4.75μ and 9.50μ. Gunther (86), in Germany, found practically the same range in normal mean diameter (6.8μ to 7.6μ). Using an ocular micrometer, Grosh and Stifel (81) found a mean diameter of 7.42μ. The greatest difference between the largest and smallest cells was 3.2μ. By a similar method Bell et al. (11) found a mean normal diameter of 7.7μ, the smallest and largest cells measuring 5.3μ and 9.9μ respectively. Wiechman and Schurmeyer (208), and Ohno and Gisevius (142), found an average diameter of 7.9μ, Medearis and Minot (132) 7.55μ, Pohle (153) 7.3μ and Wischenewsky (222) 7.2μ.

There has been some discussion regarding the diameter of cells in dry smears as compared with that found in moist preparations. Price-Jones (161) found dry cells to be somewhat smaller than cells in moist preparations although changes observed in the two preparations were parallel. Ponder and Millar (159) photographed and measured cells in plasma and found a mean diameter of 8.8μ, 1.0μ larger than that of dry erythrocytes. This unusually large diameter is questioned by Emmons (55) who emphasizes the technical difficulties of measuring cells in plasma. Emmons found cells in plasma to be actually smaller than in the dried state. Wiechmann and Schurmeyer (208), Collatz (33), and Ohno and Gisevius (142) observed no difference between dry and moist cells. Jorgensen and Warburg (109) report an average diameter of 7.7μ in moist preparations, while Holler and Kudelka (103) found an average of 7.6μ. Measuring cells of venous blood in which clotting was inhibited by means of hirudin, Gram (75) found an average diameter of 7.8μ. He used an ocular micrometer and made no selection of cells. McCormick (131), likewise using an ocular micrometer, measured cells in blood diluted with Hayem's solution and found an average diameter of 7.32μ.

This rather wide variation in the reported normal cell diameter emphasizes the importance of determining the "normal" for the technic one employs.

b. Volume of the erythrocyte

Methods of measurement. No direct means of measuring the volume of the erythrocyte with any degree of accuracy has yet been described. From the thickness of red cells, as determined by measurement of cells in rouleaux, and the diameter, the volume can be approximately calculated. In making such calculations allowance must be made for the peculiar biconcave shape of the red cell. Various formulae, such as that of Ponder (156), have been devised but none are entirely satisfactory.

By indirect methods, on the other hand, mean corpuscular volume can be determined with ease and relative accuracy. The size of the red cells of any sample may be determined in relation to an arbitrary normal by the volume index method of Capps (28), or the mean corpuscular volume may itself be calculated by dividing the volume of packed red cells per 1000 cubic centimeters of blood by the number of cells per cubic millimeter (expressed in millions). The resulting value expresses the average volume of the red cells in cubic microns (213, 218).

As an index of the mean size of cells in any sample, volume determinations appear to be superior to diameter measurements in several respects. Thus, they are simple and readily available, the volume of packed cells being determined by means of a suitable hematocrit (215). Again, since alterations in the size of cells probably take place in all dimensions, differences in size too small to be significant when only cell diameter is measured, are magnified and readily appreciated when the volume of the cells is calculated. Of the two methods of volume determination, the calculation of corpuscular volume in cubic microns is to be preferred to the determination of volume index. For the latter determination arbitrarily fixed "normal" values for volume of packed red cells and number of red cells are necessary. It is impossible to fix an accurate single normal value for these blood constituents since there is a wide variation in healthy individuals, and besides, there are significant differences between the two sexes. In the calculation of corpuscular volume no arbitrary standard is required, and, in fact, a normal variation is recognized. There is the additional advantage that, since the volume of the cells is expressed directly in cubic microns and not as an index, the actual size of the cell is more easily visualized (218).

The chief defect of these methods for the determination of the volume of red cells is that they offer no conception of the extent of anisocytosis. Where accurate knowledge in this respect is required, the calculation of mean corpuscular volume cannot replace the more time-consuming method of measuring the diameter of a large number of cells. However, information concerning variation in the size of cells more accurate than can be determined by a few minutes' examination of a smear is rarely necessary in clinical work. In actual practice, the calculation of mean corpuscular volume has proved to be of distinct value (218, 219, 220).

Normal corpuscular volume. On the basis of determinations with models of high magnification, Starling (195) gives the normal corpuscular volume as 7.22×10^{-11} cc. The average volume as calculated from simultaneous hematocrit determinations and red cell counts is 85 cu. μ and varies from 75 cu. μ to 95 cu. μ (cc. $\times 10^{-12}$) (218).

c. *Thickness of the erythrocyte*

Methods of measurement. Obvious difficulties arise in the measurement of red cell thickness. Cells may be measured directly as they lie in rouleaux, their maximum thickness being estimated in this way. Again, by calculation from a known diameter and volume their mean thickness may be determined. On the assumption that the red cell is a short cylinder, the average corpuscular thickness can be determined by the fromula,

$$T = \frac{CV}{\pi \left(\frac{D}{2}\right)^2}$$

where T is the corpuscular thickness, CV the mean corpuscular volume, and D the mean cell diameter. Both of these methods are obviously defective.

Normal corpuscular thickness. Measuring cells in rouleaux Emmons (55) found a maximum corpuscular thickness of 2.05μ, while by the indirect method, using the above formula, he found an average of 1.84μ. Employing the latter method, Gram (75) found the same value in five female and three male individuals, while I have found a mean corpuscular thickness of 1.65μ in eight individuals whose corpuscular volumes and cell diameters were normal.

d. Variation in the size of the erythrocyte in health

1. Age. There is general agreement that at birth the red cells are larger than those found in adult life. Saragea (179) found an average diameter of 8.62μ at birth and a degree of anisocytosis distinctly greater than that observed in adults. Börner (19) reports mean diameters ranging from 9.12 to 8.24μ and averaging 8.63μ in infants one to fifteen days old, while Silvette (192) found an average diameter 0.24μ greater than that found in adults (7.45μ as compared with 7.21μ). The cells of infants have been found to be distinctly larger than those of their mothers (208). Börner (19) found no reduction in size during the first fifteen days of life. Saragea (179) observed a gradual decrease in diameter until the age of two years when a very gradual increase commenced until the diameter of adult life was reached.

The work of Haden and Neff (89), and that of Mitchell (136), who determined the number of red cells and the volume of packed red cells in infants, likewise indicates the greater size of cells at this age. Calculations from data for sixty-nine infants, supplied by the latter, show an average corpuscular volume of 109 cu. μ in the first day of life, 116 cu. μ in the third day, 110 cu. μ in the seventh day, and 104 cu. μ by the tenth day.

In adults there appears to be no correlation between the size of the red cells and the age of the individual (162). Price-Jones found that an increased cell diameter in the aged was usually associated with some degree of emphysema (162).

2. Sex. Although Ohno and Gisevius (142) found the mean diameters of the cells of women somewhat higher (7.91μ) than those of men (7.77μ) the work of Price-Jones (165) and of Wiechmann and Schurmeyer (208) brings no evidence that there are significant differences between the sexes. Corpuscular volume values in men and women are almost identical (218).

3. Diurnal variation. Price-Jones (161) has demonstrated that there is a gradual increase in the diameter of the red cell during the day and a diminution during sleep. He noted variations sometimes amounting to as much as 0.6μ. Wiechmann and Schurmeyer (208) likewise have observed a diurnal variation. Haden (88), measuring corpuscular volume, was unable to confirm these observations, while Mills (135) reports an increase of cell volume during the day.

4. Exercise. Violent exercise was found by Price-Jones (161) to produce an increase in diameter of over 0.55μ and a later diminution of about the same amount. Similar effects were noted by Wiechmann and Schurmeyer (208).

5. Reaction of the blood. Price-Jones (161) has attributed these alterations in diameter to differences in the reaction of the blood. Experiments in vitro in which carbon dioxide, lactic acid, or sodium carbonate was added to defibrinated rabbit's blood, showed that red cells swell with an increase of acidity and shrink when the blood is made abnormally alkaline. Likewise the mean diameter decreased with forced breathing but rapidly returned to normal with carbon dioxide reaccumulation.

Wiechmann and Schurmeyer report (208) the average cell diameter to be less in arterial than in venous blood. In the first drop of capillary blood, according to these workers, mean diameter is similar to that in venous blood while in subsequent drops from deeper wounds the diameter is more like that of arterial cells. In general they corroborate the conclusions reached by Price-Jones (161) as also do Bell, Thomas and Means (11), and Burger (24). On the other hand, Dryerre et al. (46) point out that such conclusions cannot be made on the basis of dry smears which have been exposed to air. These workers, by a method in which cells were measured without exposure to any atmosphere other than such as would be in equilibrium with the gaseous content of the blood in the vessel from which they were withdrawn, found no difference between the mean diameter of cells before and after exercise.

Smirk's (193) observations on the influence of carbon dioxide on corpuscular volume confirm the observation of Price-Jones. Smirk found that exposure of human blood to 50 per cent carbon dioxide caused an increase of 11 per cent in the volume of corpuscles, while the addition of 100 per cent of this gas caused an increase of 17 per cent. Removal of the gas was followed by complete restoration of corpuscular volume.

6. Barometric pressure. Foerster (64) found red cells of rabbits exposed to rarefied air to have on the average a diameter of 0.4μ greater than that found under normal conditions. On the other hand, Koeppe (113) noted a decrease. Smith et al. (193 a) made simultaneous blood counts, hemoglobin and cell volume determinations at low and high altitudes. Calculation of average corpuscular volume from the figures published by these investigators shows that after a few days residence at 11,000 feet elevation a decrease of volume amounting to 4 cu. μ took place. These are the findings one would expect with decreased carbon dioxide tension in the blood on the basis of the above mentioned observations on the effect of this gas on the size of cells.

7. Dehydration. In several animals and one man subjected to absolute fast, Saragea (180) found a steady increase in the diameter of the red cells. In forty hours the cells of the man had an average diameter of "over 8.0μ." A similar increase was produced by the administration of sodium sulphate.

8. Weight, stature and surface area. A recent analysis, by the writer (217), of the correlation between the weight, stature and surface area of 100 healthy young men and 50 young women and the average volume of the red cells of their blood showed no relationship whatever between these characters.

9. Race and climate. Richardson (173), in 1877, concluded that there is no significant difference in the blood of different nationalities as far as red cell diameter is concerned. Recently Wischnewsky (222) measured the red cell diameters in 179 persons—Mongols, Persians, Turks, Finns, Caucasians—in Moscow after they had resided there a few months and presumably had become acclimatized. He found no appreciable differences between the groups.

On the other hand, Chr. Gram (71) observed that cell diameter varies somewhat with the geographical and climatic conditions surrounding the individual, red cells being considerably larger in inhabitants of northern countries than in southerners (Norway 8.5μ, Italy 7.0 to 7.5μ). Recently corpuscular volume determinations in three localities of the United States showed similar greater values in the northern areas, the average corpuscular volumes being, for men, 86.1 cu. μ in Oregon, 91.9 cu. μ in Missouri, and 79.8 cu. μ in Louisiana, while in women the mean values were 88.5, 92.8 and 80.1 cu. μ respectively (218). Although the evidence is insufficient to prove any association between climate and the size of red cells, nevertheless, since the technic followed in all three localities was practically the same, the differences may be significant.

10. Species. Interesting differences between the size of red cells in different species of mammals have been noted. In table 1 blood values for normal mammals derived from data supplied by Drastisch (39, 43), Emmons (55), Mayerson (128a) and the writer, are summarized. It is noteworthy that the size of the red cells in the various species varies inversely with the number of red cells. The variation in the size of the cells has obviously no relation to the size of the animal. Its cause is unknown.

e. Variation in the size of the erythrocyte in disease

The size of the erythrocyte has received the attention of clinicians from time to time for the past fifty years but it is only recently that its clinical importance has aroused general interest. Hayem (95) and Welcker (205) studied the diameter of the erythrocyte and S. T. Sorensen (194) as long ago as 1876 maintained that megalocytosis was characteristic of pernicious anemia. In 1903 Capps (28) pointed out that two essentially different factors influence the size of the red cell,

TABLE 1

Average blood values in various mammals

	MAN		HORSE	GUINEA PIG	RABBIT	COW	DOG	RAT	CAT	WHITE MOUSE	SHEEP	GOAT
	Males	Females										
Number of red blood cells per cu. mm. × 10^6	5.50	4.78	5.30	5.80	5.98	6.41	6.16	8.46	8.68	9.04	10.94	18.32
Hemoglobin, gm. per 100 cc.	16.21	13.91	9.60	13.85	11.50	10.55	13.01	15.40	10.70	13.90	11.80	10.27
Cell volume, cc. per 100 cc. blood	46.0	41.0	29.8	47.5	38.2	33.0	38.6	48.2	33.0	45.2	38.5	32.0
Average corpuscular volume, cu. μ.	84	86	56	82	64	52	63	57	38	50	36	17
Average cell diameter, μ.	7.7	7.7			6.6		7.2		5.6			4.0
Average cell thickness, μ.	1.8	1.8			1.8		1.6		1.5			1.3
Average corpuscular hemoglobin, γγ.	29	28	18	24	19	16	20	18	12	15	11	6
Average corpuscular concentration, per cent	34	33	32	29	30	32	34	32	33	31	31	32

namely chemico-physiologic, and what he called "biotic." Among chemico-physiologic influences he included those changes produced by hypo- and hypertonic solutions, the effects of osmosis, the influences which cause differences in the size of cells in different animals (whatever they may be) and so on. The biotic influences he grouped as anabiotic, or concerned with the growth and development of the cell, and katabiotic concerned with its destruction. Capps pointed out that the variations in the size of cells seen in the anemias were not the effects of osmosis producing larger or smaller cells but the result of biotic influences. Thus a macrocyte rich in hemoglobin cannot be produced by osmosis (which would result in the formation of a large pale cell) but is the product of abnormal cell development.

The valuable observations made by Capps were little heeded and it remained for Price-Jones (160) to attract attention to the significance of variations in the size of cells in disease.

Variations in the size of cells in disease may be considered under three heads, namely (1) megalocytosis in which group are included conditions characterized by the presence of unusually large cells, as well as by a wide and irregular variation in the size of the cells; (2) macrocytosis under which head are grouped conditions in which the cells are moderately larger than normal although the dispersion of the cells is little greater than that found in health; and (3) microcytosis, which signifies the preponderance of abnormally small cells.

Megalocytosis. Megalocytosis is most characteristically seen in pernicious anemia during the stages of relapse. In sixty-eight observations Price-Jones (163, 164) found a mean diameter of 8.31μ, while the individual cells varied from 3.75 to 13.0μ with an average variability of 12.15 per cent. The plotted curves showed a broad base with the peak swung to the right, were markedly assymetrical and dissimilar and frequently polymodal, suggesting that they were composite curves formed by two or more kinds of cells. Price-Jones has suggested that the blood in pernicious anemia contains three kinds of cells: (1) a "pernicious" type from some abnormal excitation of bone marrow; (2) normal cells; and (3) small cells resulting from the extra stimulation of bone marrow produced by the anemia.

Price-Jones (165) considers that an excessive variability is more constant in pernicious anemia than a high mean diameter and for this reason believes that methods which measure the size of corpuscles in mass and give average figures only are not of as much value as are direct micrometer measurements. This objection probably holds true for mean diameter values. On the other hand, Haden, Gram, Mills and I have found mean corpuscular volume values always greater than normal in pernicious anemia during the stages of relapse. Haden (88) reported an average corpuscular volume of 128 cu. μ in 20 cases of pernicious anemia, while in 10 cases observed by Gram (75) the corpuscular volume ranged between 136 and 94 cu. μ. Mills (135)[2] found an average of 107 cu. μ in a similar number of cases, while in 14 cases I (219) found corpuscular volume values from 164 cu. μ to 96 cu. μ at the first examination of these patients during stages of relapse. In these cases the increases in the mean diameter of the cells were similar to but not nearly as extensive as the variation in mean corpuscular volume and in several instances were not significantly greater than normal.

It is very probable that alterations in the size of cells take place in all dimensions. The observations of others do not confirm the findings of Emmons (55) who, from the examination of the blood of different species of mammals, concluded that the thickness of the red cell remains relatively constant. Ponder (158) found that the thickness of the red cells of different species of mammals varied considerably. Gram (75), calculating the thickness of red cells by the indirect method, found it to be greater than normal in all but one case of pernicious anemia, while in microcytic anemias mean cell thickness was diminished. My own observations (219) agree with those reported by Gram. The constant finding of mean corpuscular volume values greater than normal, in pernicious anemia, in spite of the presence of many small and distorted cells, is explained by the fact that, in contrast to diameter measurements, by the measurement of volume, variations in all dimensions are observed.

Although cases in spontaneous remission rarely approach a totally normal blood picture, Mediaris and Minot (132) found that with liver therapy cell diameter may become normal or even less than normal. They found that the dispersion of the red cell diameters fell well below the upper normal limit or remained slightly above normal. Price-Jones (165), by the same criteria, found the red cells normal in six cases of pernicious anemia on liver therapy while in another six cases the cells were somewhat abnormal in one or more particulars.

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[2] The values in cu. μ have been calculated from data reported by these investigators.

By noting changes in mean corpuscular volume I (219) have observed a similar gradual decrease in the size of red cells following liver therapy. Preceding the decrease in the size of the cells, a preliminary increase in mean corpuscular volume frequently occurs. The maximum values for corpuscular volume were found at the time when the reticulocyte response was greatest. That this association is causal rather than coincidental is suggested by the fact that Persons (149) has found the reticulocytes in pernicious anemia to be much larger than even the macrocytes. High normal and normal values for mean corpuscular volume are found at the time of complete liver induced remissions.

In sprue, megalocytosis similar to that found in pernicious anemia is characteristically observed and the response to liver therapy is likewise similar (219). In the anemia associated with Dibothriocephalus latus infestation megalocytosis exactly similar to that found in pernicious anemia is characteristic (107).

Macrocytosis. Although megalocytosis may very rarely be seen in some of the conditions mentioned below, this is extremely unusual and the remainder of the conditions in which abnormally large cells are found can be classed as examples of macrocytosis. In this group the dispersion in the size of the red cells is little greater than the normal variation.

Cells moderately larger than normal may occasionally be found in anemias associated with pregnancy (the so-called "pernicious anemia of pregnancy"), syphilis, and carcinoma, especially carcinoma of the stomach. Very rarely, however, is true megalocytosis found. Macrocytosis is occasionally seen in the obscure anemia of infancy, anemia pseudo-leukemica infantum. Cells somewhat larger than normal or at the upper limit of normal are also seen in aplastic anemia. In malaria high normal values are common (220).

In two cases of sickle-cell anemia, measuring one diameter of all round cells by means of an ocular micrometer, I found mean cell diameters of 8.6μ and 9.2μ respectively, with the cells varying from

6.0μ to 12.5μ. The sickle-cells themselves were about 15μ long by 2.5μ in width. Mean corpuscular volume values were normal.

Measuring the diameters of red cells in the fresh state, Rous and Robertson (175), and Ponder and Millar (159) observed that repeated large hemorrhages are associated with a small increase in the mean diameter of the cells. An increase in the scatter of the distribution of the cell sizes sometimes occurred but was an inconstant feature. In several cases of acute hemorrhagic anemia I (220) have noted a moderate increase in mean corpuscular volume. Price-Jones (163) found a decreased mean cell diameter following hemorrhage. He did not state whether the hemorrhage in these cases was acute or chronic, an important detail since the size of the red cells in the two varieties appears to differ considerably (220).

In twenty-two persons suffering from emphysema Price-Jones (162) found an average red cell diameter of 7.69μ, which figure is almost 0.5μ greater than the average he found in normal individuals. The average variability was 7.06 per cent, only slightly greater than that found in health (5.2 per cent). This increase in diameter he attributed to an increased quantity of carbon dioxide in the blood. In fifteen cases of heart failure associated with dyspnea, cyanosis, and venous congestion, Price-Jones found no increase in mean diameter (162).

Wiechmann and Schurmeyer (208) report an increased diameter during the stage of acidosis in diabetes and a return to normal with insulin therapy.

Holler and Kudelka (103) believe that the size of the red cell is influenced by metabolism and that functional disturbances of the organs of internal secretion can affect the erythropoietic system and produce changes in the red cells. In exophthalmic goiter they have occasionally observed macrocytosis and even megalocytosis, while in other diseases of the glands of internal secretion they have noted microcytosis. Meulengracht (133) has described macrocytosis in myxoedema.

In chronic interstitial pancreatitis, Holler and Kudelka (104) have observed macrocytosis and consider this finding diagnostic.

In two cases of leukemia, one chronic myelogenous and the other subacute aleukemic myelogenous, Mediaris and Minot (132) reported macrocytosis. Such a finding is unusual, however. As a general rule microcytosis is seen in the leukemias (220).

Microcytosis. Microcytosis is seen in that miscellaneous group of conditions known as "secondary anemias." In the anemia associated with various chronic infectious and "toxic" diseases the decrease in the mean diameter or mean corpuscular volume is not marked (220). The dispersion of the cells is usually somewhat greater than normal (163). In the various "blood" diseases other than pernicious anemia (polycythemia, leukemia, splenic anemia) when hemorrhage is not associated, the decrease in the size of the red cells is likewise not marked. On the other hand, in cases of chronic hemorrhagic anemia such as that resulting from hookworm infestation, bleeding hemorrhoids, amebic dysentery, and some of the "blood diseases" when chronic blood loss is associated, a marked decrease in the size of the red cells has been observed by Haden (88) and by me (220).

3. THE HEMOGLOBIN CONTENT OF THE ERYTHROCYTE

a. Methods of measurement

There is no means of determining directly the hemoglobin content of the red corpuscle. Only indirect, mean values can be calculated by the methods at present available. These calculated mean values nevertheless are of great clinical importance and in the form of the color index have been employed since the beginning of blood examination. Although when properly employed the color index affords useful information, it has come into disrepute with the realization of the incorrect and varied standards of normal on which its calculation is based and the inaccurate methods of hemoglobin estimation employed (218). The saturation index of Haden (88) suffers from similar defects.

Elsewhere a method for calculating the hemoglobin content of the red corpuscle in absolute terms has been fully described (218). The hemoglobin content of the average red corpuscle in a sample of blood, or "mean corpuscular hemoglobin," is determined by dividing the amount of hemoglobin, expressed in grams per 1000 cubic centimeters of blood, by the number of red cells, expressed in millions per cubic millimeter. The resulting value expresses corpuscular hemoglobin in micromicrograms ($\gamma\gamma$).[3] Similarly the proportion of hemoglobin in the average cell or "mean corpuscular hemoglobin concentration" is determined by dividing the number of grams of hemoglobin per 100 cubic centimeters of blood by the volume of packed red cells in the same quantity of blood and multiplying the result by 100. Corpuscular hemoglobin concentration is expressed in per cent. The constant derived by this calculation is useful rather than accurate in a physical sense since it is assumed that hemoglobin is present in the red corpuscle in the form of an aqueous solution.

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[3] A micromicrogram is a millionth of a millionth part of a gram or grams $\times 10^{-12}$.

Such direct calculations of the hemoglobin content of the red cell fall in line with the present tendency to express hemoglobin values directly in grams rather than in relation to a varying normal. As compared with the color index and the saturation index, the calculation of mean corpuscular hemoglobin and corpuscular concentration has the merits of equal simplicity, greater clarity and increased accuracy. These calculations make it possible to visualize the changes occurring in the red cell in disease much more clearly than do the indices.

Normal corpuscular hemoglobin and corpuscular concentration. The normal average corpuscular hemoglobin is 28 to 29$\gamma\gamma$ and varies from 26.5$\gamma\gamma$ to 31.5$\gamma\gamma$. The normal corpuscular hemoglobin concentration is 35 per cent and ranges from 33 per cent to 39 per cent.

b. Variation in hemoglobin content of red corpuscle in health

All available information indicates that the hemoglobin content of the red cell varies directly and quite proportionately with the size of the corpuscle. Thus, in infancy the erythrocytes are not only unusually large but contain a greater quantity of hemoglobin than is found in the red corpuscle in adult life. Calculations from the data supplied by Haden and Neff (89) for normal infants under 24 days of age, show that the corpuscles contained on the average 44$\gamma\gamma$ of hemoglobin, while Börner's (19) data for infants 25 minutes to 15 days of age, show a mean value of 39$\gamma\gamma$. Corpuscular concentration values in these infants were normal, thus indicating that the increases in volume and hemoglobin content were parallel. It is interesting to note, in passing that the red cells of pernicious anemia show a similar increase in size and in hemoglobin content with normal corpuscular concentration values.

No variation in respect to sex (218), body weight, stature or surface-area (217) has been noted for corpuscular hemoglobin or corpuscular concentration. The evidence concerning diurnal variation in corpuscular hemoglobin is inconclusive. Haden (88), who found no diurnal variation in corpuscular volume, found similarly no alteration in corpuscular hemoglobin. On the other hand Mills (135), who reported a diurnal variation in corpuscular volume, found a similar variation in corpuscular hemoglobin. It is noteworthy that the data of both investigators showed the corpuscular concentration to be relatively invariant.

Small differences in corpuscular hemoglobin were noted in the three localities of the United States for which accurate and comparable blood values are available (218). Although these differences were in the same direction as the differences in corpuscular volume already mentioned, they were not nearly as extensive. Again corpuscular concentration values showed little variation.

As between different species of mammals great differences in corpuscular hemoglobin are found (table 1). Nevertheless in spite of the great differences in the size and hemoglobin content of the red corpuscles in these animals, the values for corpuscular hemoglobin concentration are all practically equal. Such a tendency to constancy in corpuscular concentration has been also noted in disease, as will be shown in the next section. The significance of this phenomenon will be discussed later.

c. Variation in hemoglobin content of red corpuscle in disease

It is an interesting fact that, along with the increased mean volume of the red cells in pernicious anemia, there is similarly an increased quantity of hemoglobin contained in the cells. This has long been known and, in fact, it has been considered that in pernicious anemia the red cells are supersaturated with hemoglobin. This erroneous conception has probably arisen from a misinterpretation of the color index. It has been surmised that, since the color index is characteristically greater than 1 in pernicious anemia, then the cells must be supersaturated with hemoglobin. This is not true, for color index measures the quantity of hemoglobin in the average cell and not the hemoglobin saturation. Accurate blood determinations and values for the physical constants derived therefrom, show that corpuscular concentration in pernicious anemia is never greater than, may be less than, and on the whole tends to be equal to the normal concentration

(88, 219). The institution of liver therapy in pernicious anemia is followed by a preliminary diminution in corpuscular concentration below normal, and a later return to normal values (219).

In the microcytic anemias there is a decrease in the quantity of hemoglobin in the red corpuscle. This decrease is usually proportional to the decrease in corpuscular volume. Campbell (27) noted that, "in various pathological conditions changes in the concentration of hemoglobin in the corpuscle only occur to a slight extent and are relatively unimportant." Haden (88) found a significantly decreased concentration only in secondary anemias due to chronic hemorrhage. Likewise, in a large series of anemias of all types I (220) have found that corpuscular concentration values are normal, or practically normal, in all the anemias except those which are associated with chronic blood loss. In these cases significant diminutions in corpuscular concentration values are found. My own experiments indicate that changes in corpuscular hemoglobin and corpuscular volume, whether in the nature of augmentation or diminution, tend to be parallel and thus the concentration of hemoglobin in the cells remains relatively constant. This "constant" appears to be disturbed only when there is a severe, continuous drain on the hemoglobin of the body, as in chronic hemorrhage.

It is due to the fact that the amount of hemoglobin usually varies directly with the cell volume, that the color index has proved to be so useful a guide to the size of the red cells, even though cell size is not considered in the calculation of color index. It is only when the concentration of hemoglobin in the red cell is distinctly less than normal that the color index is a poor criterion of the size of the cell.

d. The manner of distribution of hemoglobin in the red corpuscle

In 1922 Bürker (25) reported observations on the basis of which he concluded that while the number of red cells and the average amount of hemoglobin in the cells of man and other mammals vary a great deal, the amount of hemoglobin proportional to each square micron of surface area of the red cell is constant, there being 32×10^{-14} grams of hemoglobin per square micron of surface area. This observation he postulated as the "law of hemoglobin distribution." ("Hemoglobinverteilungsgesetz").

Bürker's "law" has aroused an interesting controversy. Bürker assumed the red cells to be circular discs the thickness of which was negligible, and calculated their surface area on the basis of diameter measurements made from dry smears, by the formula,

$$\text{Total surface area} = 2\pi\left(\frac{\text{Diameter}}{2}\right)^2$$

Eisbrich (53), and Börner (19) following Bürker's technic and accepting his assumptions, have confirmed the latter's conclusions. Rabinowitch and Strean (168), on theoretical grounds, accept Bürker's "law." They point out that the smaller red cells are, given the same total volume of cells, the greater will be the total cell surface. These authors feel that variations in amount of hemoglobin which they have observed can be best explained on the assumption that hemoglobin is distributed on the surface of the cell. Later work from the same laboratory purporting to support this hypothesis (135) is, however, not convincing.

Brinkman and Szent-Györgyi (22) conclude that their experiments on the electrical conductivity and refraction indices of partially and totally hemolyzed blood further strengthen the view that hemoglobin is not contained within the cell but is distributed about the surface. In their experiments these authors were able to bring about a "hemoglobinolysis" without a "stromatolysis" and then, by the use of isotonic saline solution, caused the hemoglobin to be taken up by the red cells again. They consider that this points clearly to the fact that hemoglobin cannot be present in the red cells as a droplet of solution surrounded by a vesicle but that for the greater part it must be attached to the surface of the stromata. These conclusions are contradicted, however, by the recent work of Saslow (181) who can find no evidence to support the thesis that partial liberation of hemoglobin can occur.

Emmons (55), examining human blood as well as that of four other mammals, found that while the variation in number of red cells per cubic millimeter was great, the amount of hemoglobin per 100 cubic centimeters of blood was practically the same in each case. He calculated surface area on the basis of Guldin's theorems, and corpuscular volume in the manner already described. Emmons observed that the surface area of the individual red cells, calculated in this way for each species examined, gradually decreases from man to cat, while the number of cells per cubic millimeter gradually increases. The total cell surface, calculated by multiplying individual cell surface by number of red cells, he found to be practically constant in all the species. Since total amount of hemoglobin was likewise practically constant for all species, Emmons agrees with Bürker that hemoglobin is distributed according to surface area of the red corpuscle.

Emmons does not point out, however, that his figures showed that corpuscular volume, like corpuscular area, also varied inversely with the number of red cells. While the total cell volume was not as constant a figure as total surface area, the variation in this character certainly was small when compared with variation in other characters. On the basis of Emmons' own figures, therefore, there is almost as much reason to conclude that hemoglobin is distributed in proportion to corpuscular volume as corpuscular surface area.

Ponder (158) points out that Emmons' expectation that hemoglobin will vary with the cell volume if the pigment is uniformly distributed throughout the cell, but with the cell area if laid down as a surface layer, is not justified unless it is assumed that hemoglobin can exist in one concentration only. Furthermore, a linear relation between hemoglobin and surface area could exist without this necessarily referring to the position of hemoglobin in the cell. Finally, Ponder does not accept as accurate the method followed by Emmons in the calculation of surface area. Ponder's own experiments to determine the hemoglobin/area ratio show that there is "remarkably poor correlation" and much variation in different animals.

Bürker's "law" has met further criticism from other investigators. Knoll (112) points out that Bürker's assumption that the thickness of red cells can be ignored in calculating surface area is erroneous, and on the basis of his own investigations concludes that, in the case of the corpuscles of human blood, an error of 27 per cent is incurred in this way. Again, Drastich (43) points out that while Bürker assumed that he was calculating the total surface area of a red corpuscle of negligible thickness, he actually calculated the volume of a cylinder 2μ high. Thus the total surface area of a round disc 8μ in diameter and of negligible thickness is $100.6\mu^2$, while the volume of a cylinder

2μ in height and the ends of which are likewise 8μ in diameter is $100.6\mu^3$. Since the thickness of the average red cell is very close to 2μ, Drastich points out that the "constant" which Bürker observed was a constant relationship of hemoglobin to corpuscular volume. The investigations reported by Drastich (39, 41, 43) confirm such a theory. Examining the effect of decreased barometric pressure on the blood of animals (40, 42), this author observed that in splenectomized animals the increase in number of red cells was not parallel to the increase in hemoglobin or cell volume. On the other hand, hemoglobin and cell volume showed equal changes, the relation between these two values being constant. Drastich examined the blood of different animals and found that the proportion of hemoglobin to cell volume remained constant no matter how great the variations in number of red cells, hemoglobin or cell volume between these animals. He observed a similar constant relationship in the nucleated red cells of vertebrates, although not as much hemoglobin in proportion to volume was found in the blood of these animals (24 to 30 per cent) as in the blood of mammals. Drastich also noted this "constant" in the blood of normal individuals. In pernicious anemia the proportion of hemoglobin to volume was at the upper limit of normal, while in the secondary anemias he found a decrease in hemoglobin in relation to volume.

It is impossible on the basis of the information at present available to reach any final conclusion regarding the manner of hemoglobin distribution in the red corpuscle. It can be said, however, that Bürker's "law" is not proven. The relative constancy of corpuscular hemoglobin concentration in spite of wide variation in the size and hemoglobin content of red cells, already noted, indicates, rather, a constant relationship of hemoglobin to the volume of the red cell.

II. THE NORMAL NUMBER OF ERYTHROCYTES, AMOUNT OF HEMOGLOBIN AND VOLUME OF PACKED RED CELLS

1. NORMAL VALUES

In spite of the importance of accurate information concerning the normal number of erythrocytes, amount of hemoglobin and relative cell-volume of human blood, and in marked contrast to the accuracy of other less frequently employed standards, it is most surprising to find on what meagre foundation the generally accepted values for these constituents of the blood are based. The normal values for number of red cells, 5 million per cubic millimeter in men and 4.5 million in women, have been repeated from textbook without any attempt to determine their accuracy or source. Likewise the wide variation in the standards accepted as the equivalent of 100 per cent hemoglobin by the various hemoglobinometers reflects the inaccurate foundation on which they are based.

Our conceptions of the normal blood count are based on determinations made on four subjects by Vierordt (202) and Welcker (205) in 1852 and 1854 by methods which are now obsolete. It is surprising that values based on so meagre a foundation should have remained so long unchallenged. Nevertheless it is only recently that blood determinations carried out with painstaking technic have been reported in a large series of individuals known to be in good health (145, 146, 221, 214, 216). These recent blood determinations indicate the need for a revision of our conceptions of the normal.

Normal values in men

Red cell counts. Rud (177) has tabulated red cell counts reported by twenty-nine different investigators between the years 1852 and 1920 on a total of 264 normal males. Each series is very small and the average counts vary from 4.17 million to 6.08 million per cubic millimeter. Unless the methods employed were very inaccurate, some individuals who would now be considered distinctly anemic must have been included, the minimum counts being as low as 3.26 million.

More recent work indicates that the normal average value for number of red cells in men is distinctly higher than has been hitherto accepted. The average of 278 accurate determinations carried out on men 19 to 30 years of age residing in different parts of the world, given in detail elsewhere (221), is 5.57 million. Horneffer (105) has recently reported counts on 40 men of the same age group residing in Germany. His average of 4.96 million reduces the mean value so that the average of 318 accurate blood counts is 5.50 million. A noteworthy feature of all these blood determinations is the wide variation in the counts which included values below 5.0 million and above 7.0 million. The majority of the counts ranged from 5.0 to 6.5 million.

Few figures are available for men over 30 years of age. Komocki

(114) in Warsaw concluded from his examination of the blood of thirty-three men 20 to 40 years of age that the normal range in adult man is 5.5 to 6.6 million. The average in the thirty-three persons was 5.84 million.

For men 30 to 60 years of age the following accurate blood determinations have been reported:

Haden (Missouri) (88)	20 men, averaging 4.87 million
Rud (Denmark) (177)	6 men, averaging 5.42 million
Gram and Norgäard (Denmark) (76)	3 men, averaging 5.60 million
	Total, 29 men, averaging 5.06 million

For men over 60 years of age there are the following:

Rud (Denmark) (177)	7 men, averaging 5.14 million
Bing (Denmark) (15)	22 men, averaging 6.10 million
	Total, 29 men, averaging 5.87 million

Bing's counts are unusually high. Cardiac failure, emphysema, hypertension, and alcoholism have been suggested as etiological factors producing high counts sometimes found in elderly individuals. Hypertension, Bing states, was certainly not a factor in his cases. He suggests that a somewhat deficient cardiac power or local changes in skin and capillaries could more likely have been the cause of the high counts he observed.

Hemoglobin. The average of 317 accurate hemoglobin determinations made in different parts of the world on healthy men 19 to 30 years of age, given in detail elsewhere (221, 214), is 16.23 grams per 100 cubic centimeters of blood. Horneffer's (105) recent determinations carried out by the spectrophotometric method on 40 healthy men of the same age showed an average of 16.03 grams. The average of 357 accurate hemoglobin determinations on men of this age group now becomes 16.21 grams. The majority of the hemoglobin values in these individuals ranged between 14.5 and 18.5 grams.

For men 30 to 60 years of age the following values are available:

Haden (Van Slyke method) (88)	20 men, averaging 15.23 grams
Williamson (spectrophotometer) (212)	104 men, averaging 16.96 grams
Rud (Autenreith-Königsberger) (177) corrected by oxygen method)	4 men, averaging 14.35 grams
Gram and Norgäard (Autenreith-Königsberger corrected by oxygen method) (76)	3 men, averaging 15.52 grams
	Total, 131 men, averaging 16.58 grams

For men over 60 years of age there are only two reports:

Williamson (212)	81 men, averaging 15.81 grams
Rud (177)	7 men, averaging 13.66 grams

Total, 88 men, averaging 15.64 grams

Relative cell volume. The mean normal volume of packed red cells per 100 cubic centimeters of blood, derived from cell volume determinations in 231 healthy young men 19 to 30 years of age, summarized in an earlier paper (221), is 46.4 cubic centimeters.[4] To this may be added the determinations reported by Rowntree and Brown (176) for 24 normal men, of this age group. By the addition of their average of 42.8 cubic centimeters the average of 255 determinations becomes exactly 46 cubic centimeters. The majority of these values ranged between 40 and 50 cubic centimeters.

For men 30 to 60 years of age the following values are available:

Haden (88)	20 men, averaging 45.0 cc.
Gram and Norgäard (76)	3 men, averaging 47.4 cc.
Rowntree and Brown (176)	23 men, averaging 41.6 cc.

Total, 46 men, averaging 43.5 cc. packed red cells per 100 cc. blood.

In 272 normal men 20 to 49 years of age Pearl and Miner (148) report an average cell volume of 45.6 cubic centimeters.

Normal values in women

Number of red blood cells. Rud's (177) review of 293 counts reported for women between 1852 and 1920 shows, as for men, a wide variation in mean values which range between 5.59 million and 3.40 million. Each series is small and the accuracy of all the determinations cannot be affirmed. The average of more recent accurate blood counts in 186 women 17 to 30 years of age, presented in detail in an earlier paper (216), is 4.78 million per cubic millimeter. The majority of these counts varied between 4.4 and 5.3 million.

For women 30 to 60 years of age the following accurate determinations have been reported:

Rud (177)	11 women, averaging 4.90 million
Haden (88)	3 women, averaging 4.17 million

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[4] All values for volume of packed red cells here reported have been corrected for alterations in volume resulting from the addition of various anticoagulants.

Gram and Norgäard (76)	4 women, averaging 4.75 million
Komocki (114)	4 women, averaging 4.80 million

Total, 22 women, averaging 4.75 million

For women over 60 years of age there are the following:

Bing (15)	21 women, averaging 5.10 million
MacNaughton (124)	1 woman, averaging 4.60 million
Rud (177)	5 women, averaging 4.77 million

Total, 27 women averaging 5.02 million

Hemoglobin. The average of 232 accurate hemoglobin determinations on women 17 to 30 years of age, summarized in an earlier communication, (216) is 13.91 grams. The greater majority of the values ranged between 12.5 and 15.0 grams.

For women 30 to 60 years of age, the following probably accurate values are available:

Williamson (212)	93 women, averaging 15.95 grams
Rud (177)	10 women, averaging 12.68 grams
Gram and Norgäard (76)	4 women, averaging 13.36 grams
Haden (88)	3 women, averaging 13.00 grams

Total, 110 women, averaging 15.48 grams

For women over 60 years of age, there are only two reports:

Williamson (212)	71 women, averaging 15.39 grams
Rud (177)	5 women, averaging 12.39 grams

Total, 76 women, averaging 15.19 grams

The mean values for women over 30 years of age are distinctly greater than below this age. This is largely due to the fact that the values for women beyond the age of 30 years are chiefly dependent on Williamson's observations. The latter's mean value in women 17 to 30 years of age was 15.11 grams which is distinctly higher than the values reported by other investigators.

Relative cell volume. The mean normal volume of packed red cells for women 17 to 30 years of age, as calculated from determinations on the blood of 200 subjects, is 41.1 cubic centimeters (216). The addition of Rowntree and Brown's (176) average of 39.8 cubic centimeters in 12 normal women of this age group brings the mean value to exactly 41 cubic centimeters. The majority of these values ranged between 37 and 45 cubic centimeters. Cell volume determinations are available for only 19 women 30 to 60 years of age:

Haden (88)	3 women, averaging 38.7 cc.
Gram and Norgäard (76)	4 women, averaging 40.7 cc.
Rowntree and Brown (176)	12 women, averaging 39.9 cc.

Total, 19 women, averaging 39.9 cc. packed red cells per 100 cc. blood

The values presented above indicate the need for further accurate blood determinations at various ages and in different localities. The futility of attempting to express by a single value the normal red cell count, amount of hemoglobin, or volume of packed red cells, is shown by the great inter-individual differences in these characters of the blood. The causes of these differences will be discussed in detail below.

Hemoglobin coefficient and color index

For the calculation of color index 5 million is taken as the equivalent of 100 per cent red cells, while for 100 per cent hemoglobin various standards based on mean hemoglobin values found by different workers in normal individuals, are used (221). Osgood (145) has pointed out the inaccuracy of calculating color index on the basis of hemoglobin values which depend on standards derived from mean values since the standard for number of red cells in the calculation of the color index is not a mean value. He has suggested that the standard for hemoglobin be the value calculated as the equivalent of 5 million red cells, and has introduced the term "hemoglobin coefficient" to represent, "the number of grams of hemoglobin per 100 cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter." If color index is to be employed this suggestion certainly should be heeded.

In earlier papers hemoglobin coefficient values for men 19 to 30 years of age (221) and for women 17 to 30 years of age (216), have been given. Since the values for men and for women do not differ greatly it would be more practical, and almost as accurate, to employ a single value for both sexes. In the calculation of a hemoglobin standard the available accurate data for persons beyond the age of 30 years should also be included. Hemoglobin coefficients have therefore been calculated for 74 men and 18 women beyond this age for whom accurate cell counts and hemoglobin values have been reported and there is now available for the calculation of a hemoglobin standard the following material:

Osgood, Wintrobe and others (221)	274 men 19 to 30 years of age, averaging 14.61 grams
Horneffer (105)	40 men 20 to 30 years of age, averaging 16.16 grams
Haden (88)	20 men over 30 years of age, averaging 15.65 grams
Gram and Norgäard (76)	3 men over 30 years of age, averaging 13.86 grams
Rud (177)	11 men over 30 years of age, averaging 13.27 grams
	Total, 348 men, averaging 14.80 grams

Osgood, Wintrobe and others (216)	183 women 17 to 30 years of age, averaging 14.20 grams
Rud (177)	15 women over 30 years of age, averaging 12.97 grams
Haden (88)	3 women over 30 years of age, averaging 15.59 grams
Gram and Norgäard (76)	3 women over 30 years of age, averaging 14.07 grams
	Total, 205 women, averaging 14.13 grams

The average of the values for men and for women is 14.48 grams. Until further accurate determinations are available it is suggested, therefore, that 14.5 grams per 100 cubic centimeters of blood be taken as the equivalent of 100 per cent of hemoglobin. Any value for hemoglobin, expressed in grams per 100 cubic centimeters can be converted to terms of per cent in proportion to this coefficient, by multiplying by the factor 6.9.

Volume coefficient and volume index

Since 5 million per cubic millimeter is taken as the equivalent of 100 per cent red cells in the calculation of volume index, for reasons already outlined in the discussion of hemoglobin coefficient, a volume coefficient must be determined before the volume index can be employed with any accuracy. The volume coefficient is defined as, "the volume of packed red cells calculated to a count of 5 million cells" (145).

For the determination of a volume coefficient the following data are available:

Osgood, Wintrobe and others (221)	231 men, 19 to 30 years of age, averaging 41.54 cc.
Haden (88)	20 men, over 30 years of age, averaging 46.20 cc.
Gram and Norgäard (76)	3 men, over 30 years of age, averaging 42.28 cc.
	Total, 254 men, averaging 41.91 cc.

Osgood, Wintrobe and and others (216).....	175 women, 17 to 30 years of age, averaging 42.90 cc.
Haden (88)...........	3 women, over 30 years of age, averaging 46.40 cc.
Gram and Norgäard (76)...............	4 women, over 30 years of age, averaging 42.84 cc.
	Total, 182 women, averaging 42.96 cc.

The mean of these values for men and for women is 42.44 cc. It is suggested that 42.4 cc. of packed red cells per 100 cc. of blood be considered the equivalent of 100 per cent in the calculation of volume index. In any given instance the volume of packed red cells per 100 cubic centimeters, multiplied bv the factor 2.36, will express the percentage of packed red cells in proportion to this coefficient.

Reference has already been made in an earlier section (pp. 201, 212) to the advantages of calculating directly the volume and hemoglobin content of the red corpuscle as compared with indirect volume index and color index determinations (218).

2. THE INFLUENCE OF AGE AND SEX ON NUMBER OF RED CELLS, AMOUNT OF HEMOGLOBIN, AND VOLUME OF PACKED RED CELLS

The blood in infancy and childhood. Striking differences in the content of the blood in the early years of life have been repeatedly noted. Sorensen (194) first called attention to the high erythrocytic content of the blood of newborn infants. His observations were confirmed by those of Hayem (94), Gundobin (85), Otto (147), Schiff (186) and Aitkin (2). Engelsen (57) found an average of 6.24 million red cells in 40 newborn infants with no difference between males and females or between full-term and premature infants. Fehrsen (60), examining the same number of infants, found in the first two hours after birth an average of 6.05 million, which gradually dropped to 5.5 million ten days later. Williamson's (212) careful hemoglobin determinations showed an average of 23.25 grams per 100 cubic centimeters of blood in 31 infants one day old. This high figure fell only very slightly in the first two weeks of life. Of more recent work may be mentioned Mayers' (128) average of 7.63 million in forty-one infants examined during the first two hours of life and the reports of Lucas et al. (121), Sanford (178), and Mitchell (136), who found 5.5, 5.8 and 5.7 million cells respectively in the first day of life and a drop of 1.4 to 0.7 million during the next ten days.

Hayem (94) suggested that the high counts found in infancy were associated with late closure of the cord while Schiff (186) believed that they were due to loss of fluids and consequent concentration of the blood. Mayers (128) and Lippman (120), on the other hand, have been unable to confirm the earlier observations that changes in number of red cells were correlated with changes in weight. Lippman observed the high red cell count even in infants in whom loss of weight was successfully prevented by means of complementary feedings.

Like several other observers (Neumann and Kolliker (141), Fehrsen (60), Lucas et al. (121)), Lippman noted nucleated red cells, polychromatophilia, anisocytosis and poikilocytosis in the first few hours of life. He suggested that bone marrow activity is an important factor in causing the initial high red cell count. The abnormally large size of the red cells in infancy has already been discussed in detail (p. 202).

While no large series of accurate blood determinations is available, there is general agreement that, following the initial high red cell and hemoglobin content during the first few hours after birth, there is a steady decrease in the number of cells and amount of hemoglobin. In the first two weeks of life this drop is very gradual but after this time more rapid changes take place to reach a minimum variously reported as 4.0 to 5.0 million red cells (60, 128, 177) and 12.5 grams of hemoglobin (212) at about two years of age, when these constituents again begin to rise rapidly during the first few years and then more slowly until the values found in adult life are reached at about the age of puberty. Until the age of puberty no appreciable difference between the two sexes has been noted (21, 177, 4).

Old age. Blood values at different stages of adult life have already been given. From the meagre accurate reports available no conclusions concerning any significant differences associated with old age can be drawn. Pearl and Miner (148) in an analysis of cell volume determinations in 272 normal males 20 to 49 years of age found no significant correlation between cell volume and age.

It has been stated that after the climacteric blood values in the two sexes again tend to be the same. The small amount of accurate information which is available does not support this conclusion.

The influence of menstruation. Statements in regard to the influence of menstruation on the blood of normal women are conflicting and the data offered in their support are unconvincing. Sfameni (190), examining the blood of six women, found a pre-menstrual rise and intramenstrual fall of red cells and hemoglobin. The drop in the number of red cells amounted to 0.22 million and was slowly regained after menstruation. Maurel's (127) experience was similar to that of Sfameni. Ewing (59) quotes a number of investigators who found a slight increase in red cells and hemoglobin after normal menstruation and referred this result to stimulation of the blood forming organs. Pölzl (154) and Eichman (48) are quoted by Rud (177) as having found a constant increase prior to and during menstruation. Terhola (201) and Rud (177) found no appreciable change associated with menstruation.

TABLE 2

Blood findings in 48 normal young women grouped according to relation to the menstrual period

TIME EXAMINED	DAYS AFTER END OF LAST PERIOD	NUMBER OF SUBJECTS	RED BLOOD CELLS		HEMOGLOBIN	CELL VOLUME	MEAN CORPUSCULAR VOLUME
			Average	Standard deviation			
			millions		*grams per 100 cc.*	*cc. per 100 cc.*	μ^3
During menstrual period	0	6	5.05	0.34	13.30	39.3	78.1
Post-menstrual	1–7	15	4.80	0.29	13.70	39.1	80.3
Inter-menstrual	8–17	19	4.90	0.24	13.78	39.3	80.4
Pre-menstrual	18+	8	5.02	0.26	13.98	40.4	80.5
General average			4.93	0.28	13.76	39.5	80.1

In interpreting the results of these and similar investigations, it is important to make due allowance for the error involved in making these blood determinations. Even when unusual care is taken in making red cell counts there is a probable error of at least 2 per cent involved, which, for a count of 5.0 million cells, is equivalent to 0.1 million (221). By the statistical rule that a difference between the two quantities of three times the probable error entailed in their determination is probably significant, while a difference of four times that error is certainly significant, it is apparent that differences in red cell counts of less than 0.3 to 0.4 million cannot be considered as having any significance. Similar criticism applies to small observed differences in hemoglobin content.

In table 2 blood findings in 48 normal women examined by me (216) are grouped in relation to the menstrual period. Considering probable errors, no importance can be attached to the small differences observed.

The influence of pregnancy and lactation. Whether pregnancy per se has any influence on the blood still remains in doubt in spite of a rather extensive list of reports on the subject.

Anemia is frequently observed in pregnancy. Besides distinctly pathological conditions, a mild anemia has been reported by many observers (110, 123, 65, 17) some of whom consider this mild anemia to be "physiological." Gram (73), several years ago, came to this conclusion in regard to the earlier months of pregnancy. A recent study by Bland Goldstein and First (17) showed that only three of two hundred pregnant women had red cell counts greater than 4.2 million. Since etiological factors such as infection and toxemia did not seem to be necessarily associated and, furthermore, since a large proportion of these were private patients living under good environmental conditions, these writers concluded that factors connected with the gravid state must be in some way responsible for the anemia.

It has been suggested that a condition of hydremia associated with the increased vascular area exists in pregnancy (209, 96), that the anemia is caused by the withdrawal of iron by the fetus (17), or that a "syncytial hemolysin" is the cause (101). The entire subject has been inadequately studied. A rapid recovery soon after delivery has been noted in most cases of pregnancy anemia.

No appreciable change in the blood has been observed during normal lactation that is not unduly prolonged.

3. CONSTITUTIONAL INFLUENCES CAUSING VARIATION

Race. From the few accurate determinations made on individuals of different races, no conclusions regarding any racial variation in the number of red cells, amount of hemoglobin or relative cell volume can be drawn. Maurel (127) concluded that racial differences, if actually present, are scarcely appreciable. Glogner (68) found a somewhat higher count in 30 natives of West India as compared with 51 Europeans residing there, while M'Cay (129) reported higher cell counts in Bengalis as compared with those found in a number of Europeans resident in India. Climatic influences may perhaps operate to produce differences between races. This matter will be dealt with later.

Influences of body weight, stature and surface area. The blood values for 100 men and 50 women examined in Louisiana have been studied with the object of determining the relation between variations in body build and variations in the blood constituents (217). This analysis showed that individual differences in number of red cells, amount of hemoglobin and cell volume were, in gross, slightly correlated with individual differences in body weight, stature and surface-area. The sign of correlation was positive; that is, these constituents of the blood tended to be greater in amount in heavier and taller individuals. However the regressions of these variables upon each other was quite small in amount as compared with the range of difference in these characters observed in normal individuals.

Influence of complexion. In the tropics red cell counts and hemoglobin values in blonde and brunette types have been compared. Neither the investigations of Chamberlain (31) nor those of Breinl and Priestley (21) show any difference between these two types.

4. DIURNAL AND TEMPORARY INFLUENCES

The diurnal variation. A diurnal variation in the number of red cells and amount of hemoglobin has been observed by many investigators. While in the earlier reports (87, 171) variations in red cells as great as one million were described, more recent investigations indicate that the diurnal variation does not exceed 5 per cent (203) while the differences in hemoglobin amount to 10 or 15 per cent and occasionally 30 per cent (44, 167). There is general agreement that red cells and hemoglobin are found in greatest quantities in the waking hours and gradually decrease in amount during the day (203, 170, 44, 177). The relative cell volume, on the other hand, appears to change very little throughout the day (72, 177). In Rud's (177) series, red cell counts on the same individuals at the same time of the day showed no appreciable variation throughout several months.

The cause of the diurnal variation has not been fully explained.

The influence of digestion and exercise has been considered (118), but neither diets consisting of constant amounts of solid and fluids, and meals given at definite periods of the day, nor even rest in bed with the minimum essential muscular movements, had any effect on the variation curves (168). Rabinowitch (168) observed, however, that in patients with advanced heart failure there was a marked fixation of the hemoglobin curve, while Mills (135) found a lessened variation in various anemias. Dreyer and his co-workers (44) believe that the variations are closely connected with variations in pulse rate, blood pressure, rate and volume of respiration, and possibly with fluid absorption or kidney secretion.

Digestion, water administration, dehydration. Early observations on red cells and hemoglobin after meals indicated that there was an immediate rise following the meal (194), a decrease one-half to one hour after the meal (202, 72, 127, 170, 37), and after several hours another rise (189). Oliver (143) in 1892, found lower cell counts half an hour following a meal even when water was withheld. This observer found the variations to correspond with fluctuations in the "digestive lymph wave," the cell count being lower when the amount of fluid in the tissues was greatest, and vice versa. A recent investigation by Rud (177) failed to show significant variations in red cells and hemoglobin following meals. On the other hand, Greene and Rowntree (77) recently reported rapid and progressive diminution of hemoglobin concentration in the blood following administration of water by mouth.

It has been repeatedly stated that fasting is followed by an increase in the number of red cells in man and animals (127, 25a). Hayem (95) found that a twenty-four hour fast resulted in a gain of 0.4 to 0.5 million cells. On the other hand, other observers have noted a distinctly anemic condition produced in healthy men after fasting (59).

Recently experimental dehydration in animals has been shown to produce an increase of red cells and hemoglobin, the degree to which this occurs depending on the rapidity with which fluid is lost from the body (126). Gram (74) has found the increase in hemoglobin to be roughly one-half the increase in serum proteins.

Phalen (150) studied the influence of clothing on the red cell count. He found that variations in cell counts were associated with the degree to which the garments induced perspiration.

Diet. The influence of diet on regeneration of the blood in the anemias has been thoroughly investigated by Whipple (206) and others. An unbalanced and insufficient diet which is maintained for some time will undoubtedly have derogatory effects on the blood of a normal individual. Whether less striking variations in diet result in changes which are appreciable has not been determined. More than half a century ago, Hayem (95) stated that meat eaters averaged a higher percentage of red cells than vegetarians. Cornell (35) has found liver diet to have no effect on the number of erythrocytes in normal individuals, while Watkins et al. (204), Smith and Whitby, (193b) and Neidhardt and Bannasch (140) have reported definite and in some cases, marked increases.

Exercise. It was early observed that active muscular exercise provokes an increase in the peripheral erythrocyte count. Hawk (93) found an average gain in erythrocytes of 21 per cent following swimming, 16.6 per cent after sprinting, 12.9 per cent after walking, and 12 per cent after bicycling. The studies of Willebrand (210) and of Zuntz and Schumberg (224) indicated that this increase stands in inverse ratio to the length of the period of exercise. Edgecomb (47) found that active exercise caused a slight overproduction, while passive exercise produced no change. Mitchell (137), however, reported that massage increased the corpuscular richness of the blood. Hayem (95) noticed that labor carried to the point of fatigue resulted in a marked decrease in the number of corpuscles, and Cohnheim et al. (32) as well as Gross and Kestner (82) found a decrease in cells and hemoglobin after long and strenuous mountain climbing.

In explanation of these changes, it was suggested (37) that exercise is followed by increased blood pressure which not only inspissates blood but also disseminates peripherally many cells which hitherto have lain inactive in the deeper circulation (93). It was also suggested that fluid is lost into the muscles (210) or liver lymphatics (79).

More recent investigations have confirmed these earlier observations. Schneider and Havens (188) have found the immediate influence of physical exertion upon the blood of the periphery to be one of concentration with an increase of hemoglobin amounting to 3.5 to 10.9 per cent, and red cells 3.2 to 22.8 per cent, and a proportionate increase of specific gravity. This is followed after the cessation of the exertion by a dilution of the blood and fall in hemoglobin, red cells, and specific gravity. These workers have further observed that abdominal pressure and massage raise the content of hemoglobin and red cells in the peripheral stream, and abdominal pressure following exertion prevents dilution to a large measure. According to Schneider and Havens exercise at high altitudes is followed by no increase of cells or pigment while abdominal massage and exercise cause dilution of the blood.

In contradiction to these findings which suggest that exercise calls forth a supply of red cells from some storehouse, probably located in the abdomen (10), Boothby and Berry (18) find that the percentage of hemoglobin and number of red blood cells increase under conditions of work causing an appreciable amount of perspiration, but not otherwise.

Broun (23) has published a series of instructive experiments on the effect of exercise on the blood of dogs. This worker measured number of red cells, hemoglobin, relative cell volume (hematocrit) and total blood volume (by the carbon monoxide and dye methods). He found that ten to fifteen minutes of active exercise caused usually a slight increase of plasma volume and quite regularly a marked increase in cell volume, hemoglobin, pigment volume, and number of red cells, the increase of cell volume being the greatest of the three. After several hours of exercise, plasma volume consistently showed an increase, while cell volume showed a decrease below the average volume found after ten minutes of exercise. Hemoglobin and total pigment volume decreased even more, although still remaining definitely above the level maintained before exercise commenced. Red cells also decreased in number.

These findings indicate that the initial concentration of blood during exercise is not due to loss of fluid, since there is no decrease in plasma volume, but is probably the result of a redistribution of cells. The increase in volume of plasma may be due to fluid taken from the muscles (83). The decrease in total cell volume and pigment volume during prolonged exercise Broun considers to be due to blood destruction, a process which begins with the commencement of exercise, but is masked in the early stages on account of the redistribution of cells which takes place. In dogs long maintained under sedentary conditions a great decrease in total circulating hemoglobin and red cell volume occurred when they were exercised vigorously during several consecutive days. This was interpreted as the result of increased blood destruction, unrepaired for the time being. A definite increase in the percentage of reticulocytes was observed, after exercise, in animals previously kept to a sedentary life. Replacement, by transfusion, of blood destroyed during exercise prevented the reticulated cell reaction. Similarly, animals rendered plethoric and then exercised showed no increase in reticulated cells as long as the plethora persisted. Thus exercise appears to be an important factor in the maintenance of an efficient hematopoietic tissue.

Training is apparently very important. Animals recently caged did not show as great a decrease in cell volume after exercise as those confined for several months. Again in "sedentary" dogs put on strenuous exercise, by the third week of exercise the loss had been made up, suggesting an adaptation of the hematopoietic system to the increased demands made by this increased destruction.

Drinker et al. (45) found that exercise, coupled with artificial marrow stimulation, did not cause an increase of young forms in the blood of experimental animals. Likewise Isaacs and Gordon (106) examining marathon runners following a period of training and just prior to the race, found an increased number of young red cells in the blood, which, however, was not further augmented by the effect of the race, nor was the character of the mature cells changed. From this it appears that training is associated with a slightly lowered threshold of blood cell delivery which is not affected by exercise itself.

The work of Barcroft and his associates (10) indicates that the chief source of the early supply of red cells following exercise is probably the spleen. Scheunert and Krzywanek (184) have found the initial increase in number of cells following exercise to be absent in splenectomized animals.

Vasomotor and psychic influences. Emotional polycythemia. Following the application of cold, high counts are found in the peripheral blood which have been explained as being due to either a diminished dilution of the blood by plasma from the subcutaneous tissue, or to local stasis (84).

Ferrari (61) was the first to study the influence of emotional excitement on the blood count. Blood counts in students just after an examination were found on an average 0.46 million greater per cubic millimeter than before the examination, the highest counts corresponding to the most excited, the lower ones to the more phlegmatic. Lamson's (115) experiments in cats showed similar results which, however, failed to occur after the adrenals had been removed. He concluded that either red cells were liberated by the liver, or plasma was absorbed into the hepatic capillaries and in this way concentration of the blood was produced. Schneider and Havens (188) found that adrenalin administered by mouth caused the blood in the peripheral capillaries to be concentrated. Hess (98) found that a redistribution of blood followed adrenalin injection, there being an increase of cells in the arterial (and later venous) blood, and a concurrent decrease in the capillary stream.

The recent developments in the knowledge of the spleen have stimulated new interest in emotional polycythemia. It has been now definitely shown that the spleen is a reservoir for red cells (10) and that muscular exercise and the injection of adrenalin (20) and pituitrin, among other factors, cause the spleen to contract. Even slight affective stimuli such as clapping the hands, pinching the skin and display of food cause contraction of the spleen in dogs (91) and anxiety and jealousy in dogs have been found to be associated with diminution of spleen volume (10). These observations suggested to Izquierdo and Cannon (108) that emotional polycythemia is produced by liberation of adrenalin and consequent contraction of the spleen.

Their experiments support these conclusions. Emotional excitement in cats produced immediate increases of cell counts far in excess of the normal variation, which began to decrease soon after the source of excitement was removed. Hematocrit and hemoglobin determinations did not show as much increase as the erythrocyte count, which suggests that smaller cells are liberated after excitement. After removal of the upper abdominal sympathetic strands and bilateral severance of the splanchnic nerves, emotional polycythemia failed to occur. If only the liver among the upper abdominal viscera was left innervated, excitement caused no noteworthy hyperglobula. Inactivation of the adrenal medulla had no marked influence on emotional polycythemia.

5. CLIMATIC INFLUENCES

Low barometric pressure. The response of the blood to the influence of low barometric pressure has been the subject of much experimentation and no little controversy. There is now general agreement, however, that the usual response to ascent of high altitudes is a rapid increase in the number of erythrocytes and amount of hemoglobin (78). The rapidity of this primary increase depends chiefly on the rate and height of the ascent, but also on the physical condition of the subject and the amount of physical effort expended. Individual differences have always been observed and the response following a fatiguing climb has been shown to be distinctly less than normal (187.)

Following the primary increase there is a more gradual readjustment to the new living conditions which requires several weeks and even months to establish itself. The rise in hemoglobin is probably proportional (187). FitzGerald (62) stated that among acclimated individuals for every 100 millimeter drop in barometric pressure there is a rise of 10 per cent in hemoglobin.

In individuals constantly living at high altitudes high figures for cells and hemoglobin are constantly found (6), and it is interesting to note that physical differences in these individuals have been observed. In the Andes expedition an increase in the width of the chest in proportion to the height, and a lessened rib slope (as determined by x-ray) were noted in natives of these high altitudes (6).

The mechanism of the adjustment of the blood to low barometric pressure is still a matter of dispute.

(1) Many believe that the early increase in hemoglobin and corpuscles is apparent rather than real and is to be attributed to concentration of the blood, that is, a reduction of the total blood volume. Such a theory is, however, contradicted by the fact that changes in number of red cells may be found in even as short a time as 20 to 30 minutes, during which time perspiration has not noticeably increased (78). Birley (16) points to the complaint of over-filling of the bladder among aviators on long patrols as evidence of concentration of the blood. Other investigators (78) do not consider this evidence as sufficient since the phenomenon is not noted in all individuals. Experimental exposures to low oxygen have shown no polyuria. Finally,

there is no experimental proof that during low oxygen tension the muscles absorb a larger volume of water (78).

(2) The existence of a reserve or dormant supply of erythrocytes has been suggested as the source of the early supply of red cells. The work of Schneider and Havens (188) is very interesting in this connection. These authors found that abdominal massage and exercise at low altitudes increased the number of red cells and hemoglobin in the peripheral capillaries; at high altitudes before any adjustment had occurred, massage and exercise had the same effect; after partial or complete acclimatization, however, massage and exercise lowered rather than increased the number of cells and hemoglobin.

The work of Barcroft and others has shown that the spleen is a storehouse for red cells, the "doors" of which can be unlocked by hemorrhage, oxygen want, carbon monoxide (10), exercise (1,184), adrenalin, (20) and suffocation (14). It is likely that this reserve is called upon when an individual is subjected to a relatively sudden change in barometric pressure. Giannini (67) has recently reported that in splenectomized rats, guinea-pigs and rabbits, rarefaction of the air they breathed was followed by a much smaller increase in the number of erythrocytes than in normal animals. Both the absolute and the relative increase of hemoglobin, however, was greater following splenectomy.

(3) Lengthening of the life of the erythrocyte is a possible explanation for the immediate increase in number of cells, but there is no experimental proof to favor this hypothesis.

(4) Finally an increased hematopoietic activity of the bone marrow must be considered. During the expedition to the Peruvian Andes, a marked increase in the number of reticulocytes was noted (6), which number fell to normal after the descent. No nucleated cells were seen. In natives the ratio of reticulated to unreticulated red cells was not found to be greatly increased, but their absolute number per cubic millimeter was about 50 per cent greater than normal. Barcroft believes that this suggests bone marrow hypertrophy in acclimated individuals. Numerous attempts have been made to find nucleated red cells in the blood following ascent to high altitudes, but many have been futile (187).

Smith and his associates (193a), in carrying on blood volume determinations by the dye and carbon monoxide methods, found no evidence of abrupt changes in red blood cells or blood volume but noted a definite increase after the first few days spent at a high altitude. Like Koeppe (113), who found a decrease in the size of erythrocytes at high altitudes, these workers found that the hematocrit volume rose less than the percentage of red cells. They concluded that the increase in cells and hemoglobin is due to the production of more cells, not to a redistribution. Further evidence favoring the theory that bone marrow activity is stimulated, is brought by Drastich (40) who found cells of lower hemoglobin content and therefore, as he believes, new young cells in the blood of animals subjected to a low oxygen tension. In splenectomized animals he observed (42) that the increase in cells occurred more slowly. Once the increase was established, however, the drop in count consequent to the return to normal oxygen tension followed more slowly. Furthermore in the splenectomized animals the increase of cells was associated with an increase in the number of large cells.

It is possible that research on the influence of irradiation on the blood will add new light on the subject of the blood at high altitude. Kestner (111) considers that the effective factor of high climate is not diminished oxygen content but increased and more intense radiation by the sun's rays.

Influence of climate, temperature and season. The absence of the fresh color of the cheeks and the "picture of health" in individuals residing in tropical and subtropical regions is one of the first observations of the visitor, both lay and medical. This pale, languid appearance, which is to be seen even in the southern United States in individuals who are otherwise in good health, has led to the conception that a tropical or subtropical climate affects the blood in such a way as to produce a "tropical anemia."

This conception that a physiological anemia exists in the tropics has maintained its hold on the imagination of medical men (116) and laymen, in spite of a number of investigations which contradict this theory. Among the first contributions of scientific value to tropical physiology have been made in the realm of blood morphology (199). In 1884, Maurel (127) concluded that, instead of decreasing, the red cell count rose on first reaching a tropical climate and later returned to the normal figures of temperate climates. A few years later, Marestang (125), while admitting the logic by which it was concluded that a physiological anemia existed in the tropics, pointed out that the observations made on two individuals by Hayem, and Jousset, and the figures supplied from Brazil where beriberi was endemic by Pedro de Magalhaes, on which these conclusions had been based, were too few. His own determinations on 29 white residents of Polynesia showed an average count of 6.18 million. Marestang even ventured to suggest that the lower oxygen tension of the warmer air of the tropics caused an increase of red cells and hemoglobin and predicted that the same condition would be encountered at high altitudes.

The investigations conducted by van der Scheer (183), Eijkman (49), Glogner (68), and Plehn (152), as well as more recent determinations, likewise seem to refute the existence of an anemia of purely climatic etiology. Cuthbert (36) found an average count of 5.5 million red cells in 21 European soldiers who had resided for many years on the west coast of Africa. Wickline (207) reported in 1908 a series of carefully made examinations of the blood of about 90 officers and men who were known to be in good health. After a sojourn in the Philippines of almost two years' duration an average count of 5.64 million red cells was found, the red cells having increased in number during the period of observation, while the hemoglobin was somewhat lower than at the time of their arrival. A few years later, Chamberlain (31), in an extensive investigation of the blood of 687 American soldiers who had resided in the Philippines for 20 months, found 50 per cent of the counts to range between 5 and 6 million, and 13 per cent above this figure. The average was 5.20 million.

Breinl and Priestley (21) examined the blood of 580 children of both sexes between 7 and 16 years of age who had resided all or practically all of their lives in northern Australia where the climate is tropical and subtropical. An average of 5.08 million red cells was found.

The only low values for cells or hemoglobin which I have been able to find are those of Hernandez (97), in Venezuela, who reported an average red cell count of 3.25 million in 25 supposedly healthy young medical students; Sierra, (191) who found an average of 4.55 million in 15 students in Venezuela; and Lippincott, (119) who concluded, as a result of red cell and hemoglobin (Tallquist) determinations on hos-

TABLE 3

Blood determinations in tropical and sub-tropical climates—males

AUTHOR	YEAR	LOCATION	NUMBER EXAMINED	RACE	OCCUPATION	LENGTH OF RESIDENCE	AGE	RED BLOOD CELLS × 10^6			HEMOGLOBIN	
								Average	Maximum	Minimum	Amount	Method
						years	*years*					
Maurel (127)	1884	West Indies	7	White	Soldiers	0.5–1.1		5.45	6.00	4.98		
Maurel (127)	1884	West Indies	4	White	Soldiers	5–13		4.96	5.40	4.30		
Maurel (127)	1884	West Indies	9	Hindu	Laborers	Life		5.08	5.90	3.60		
Maurel (127)	1884	West Indies	6	Black	Laborers	Life		5.13	5.80	4.30		
Van der Scheer (183)	1890	East Indies	2	Yellow	Laborers	Life		6.02	6.40	5.60		
Marestang (125)	1890	Polynesia	17	White	Prisoners	5–17		5.77	7.16	4.20	14.35 grams	Malassez
Marestang (125)	1890	Polynesia	12	White	Soldiers	2		6.76	7.80	5.60	14.20 grams	Malassez
Eijkman (49)	1891	East Indies	6	Malay	Students	Life	18–23	5.62	5.70	5.15	100 per cent	Fleischl
Eijkman (49)	1891	East Indies	9	Malay	Laborers	Life	28–50	5.00	5.60	4.48	94 per cent	Fleischl
Eijkman (49)	1891	East Indies	21	White	Doctors and soldiers	2.5–14	21–39	5.36	5.80	4.90	100 per cent	Fleischl
Glogner (68)	1892	East Indies	51	White	Soldiers	0.7–30	18–48	5.26	6.32	4.32	99 per cent	Fleischl-Meischer
Glogner (68)	1892	East Indies	30	Natives	Laborers and soldiers	Life	20–36	5.58	6.56	4.80	106 per cent	Fleischl-Meischer
Hernandez (97)	1893	Venezuela	19	White	Students	Life	16–20	3.25	3.80	1.90		
Wickline (207)	1908	Philippines	17	White	Officers	1.7		5.51			87 per cent	Fleischl-Meischer
Wickline (207)	1908	Philippines	64	White	Soldiers	1.7		5.28			82 per cent	Fleischl-Meischer
Chamberlain (31)	1911	Philippines	65	White	Soldiers	2.3 av.	26 av.	5.15			90 per cent	Dare and Fleischl-Meischer

Chamberlain (31)	1911	Philippines	601	White	Soldiers	1.5	28 av.	5.21	7.00+	4.00−	90 per cent	Dare and Fleischl-Meischer
Cuthbert (36)	1911	Africa	18	White	Soldiers	1	17–21	6.02	7.14	4.80	100 per cent	Gower
Sierra (191)	1926	Venezuela	15	White	Students	Life	17–21	4.55	5.70	3.70		
Lippincott (119)	1927	Mississippi	639	White	Patients			4.54			85 per cent	Tallquist
Lippincott (119)	1927	Mississippi	232	Black	Patients			4.43			83 per cent	Tallquist
Wintrobe and Miller (221)	1929	Louisiana	100	White	Students	3–30	19–30	5.85	7.53	4.70	17.0 grams	Newcomer-Van Slyke

TABLE 4

Blood determinations in tropical and sub-tropical climates—women and children

AUTHOR	YEAR	LOCATION	NUMBER EXAMINED	RACE	OCCUPATION	LENGTH OF RESIDENCE	AGE	RED BLOOD CELLS × 10⁶			HEMOGLOBIN	
								Average	Maximum	Minimum	Amount	Method
						years	*years*					
Maurel (127)	1884	West Indies	9	Hindu	Laborers	Life		4.18	4.80	2.79		
Maurel (127)	1884	West Indies	5	Black	Laborers	Life		4.26	5.27	4.00		
Breinl and Priestley (21)	1914	N. Australia	305	White	Male children	Life	7–16	5.05	6.00+	4.00–	12.31 grams	Fleischl-Meischer
Breinl and Priestley (21)	1914	N. Australia	269	White	Female children	Life	7–16	5.11	6.00+	4.00–	12.66 grams	Fleischl-Meischer
Lippincott (119)	1927	Mississippi	779	White	Patients			4.25			82 per cent	Tallquist
Lippincott (119)	1927	Mississippi	226	Black	Patients			4.14			81 per cent	Tallquist
Wintrobe (216)	1930	Louisiana	50	White	Students	3–30	17–30	4.93	5.65	4.45	13.76 grams	Newcomer-Van Slyke

pital and clinic patients, that the normal average hemoglobin percentage and erythrocyte counts are lower in Mississippi than the usually accepted standards. The accuracy of the determinations reported by Hernandez must be held in doubt, and certainly the validity of reaching conclusions regarding "normal" on the basis of blood examinations made on hospital and clinic patients is very questionable.

Investigations of the blood of healthy young men and women in Louisiana were primarily undertaken by me in order to study this question of tropical anemia. Details of these determinations have already been published, (221, 214, 216) and it need only be pointed out here that the number of red cells and amount of hemoglobin in the men were distinctly greater than the values found in the north, while the results for women were slightly, though not significantly higher than those found in Oregon (145, 146).

Consideration of the blood findings listed in tables 3 and 4 forces one to the conclusion that the conception that a tropical or subtropical climate produces an anemia, is a myth. The pallor of individuals residing in these localities is unquestioned, but must be explained on some other basis.

It has been suggested that conditions in tropical climates favor an activity of the erythropoietic system beyond limits set by climatic conditions in colder regions. Some of the determinations reported from tropical climates which have been tabulated above show average figures higher than those generally accepted as normal. Marestang's (125) suggestion that the lower oxygen tension of warm air stimulates red cell production, has already been mentioned. Wolfe, and Wickline (207) suggested that in the tropics heat and light stimulate formation of red cells. In hot desert climates Schieffer (185) and later Wohlgemuth (223) observed a rise in the red count. Sundstroem's (200) experiments tend to support the contention that the number of red corpuscles in the peripheral blood may, in some instances, undergo an increase in a tropical environment, which he considers is due to stimulation of the blood forming organs as well as to inspissation of the blood. He quotes Barcroft (9) as having found an increase in the number of reticulocytes in a hot environment.

Whether a higher content of red cells and hemoglobin is actually present in hot climates remains to be proven. Osgood's work in Oregon (145, 146) suggests that the generally accepted normal values for red cells are too low and so it is possible that the difference between determinations in hot and colder climates is more apparent than real.

In order to determine whether or not the high values found in the men examined in Louisiana (221) were the effect of season, these determinations were repeated during the coldest season of the year in 25 of the 100 persons originally examined. Nineteen of this number were volunteers, unselected in any way, while the remaining six were individuals who showed unusually high red counts at the first examination. The results of these determinations are shown in table 5, from which it can be seen that there is no significant difference between the findings in summer or winter. This is in agreement with the report of Breinl and Priestley (21) that season had no influence on the average blood counts performed in children in Australia. It is interesting to observe that the blood findings in the six men who showed unusually high figures at the first examination were on the whole distinctly lower at the second examination, although still greater than the general average.

TABLE 5

Determinations in summer and winter compared

SUBJECTS EXAMINED	RED BLOOD CELLS	HEMOGLOBIN	CELL VOLUME	INDEXES		
				Volume	Color	Saturation
	millions	*grams per 100 cc.*	*cc. per 100 cc.*			
100 men, summer, 1928	5.85	17.00	46.5	0.97	1.00	1.02
25 men, winter, 1929	5.84	16.82	47.2	0.98	0.99	1.00
19 unselected men, winter, 1929	5.74	16.70	47.1	1.00	1.00	1.00
6 highest men, summer, 1928	7.00	18.15	48.4	0.85	0.89	1.04
Same 6 men, winter, 1929	6.16	17.06	47.7	0.93	0.95	1.02

The cause of "tropical anemia." Since it appears that the pallor so noticeable in healthy residents of warm climates cannot be explained on the simple basis of a physiological anemia, it is interesting to speculate on the cause of this striking effect of tropical climates. The effect of shorter light rays on the skin and the process of pigmentation, the lack of stimulating winds and invigorating cold, different habits of diet and life with their resulting effect on metabolism, are only a few of a large number of possibilities.

Eijkman (52) who has had a large experience in tropical physiology, points out that in the cooler regions it is only the regularly uncovered skin, directly exposed to the influences of weather, that is generally distinguished by richness of blood. The covered skin, which is usually pale, may be said to be in an artificially produced tropical climate. Lehman and van der Scheer (117), and Musgrave and Sison (139) consider the pallor of the skin to be a local vasomotor condition. The latter workers have found blood pressure to be lower in tropical climates and suggest that this as well as the pale appearance can be explained on the basis of a diminished peripheral resistance. They further point out that the "anemia" is a very evanescent one which very readily disappears on transferring to a colder climate.

The contention that the anemic appearance is due to ischemia of the skin capillaries (30) can scarcely be held as being probable since a large blood supply is needed for one of the most important functions of the skin in hot climates, namely sweating.

Strong (198) suggests that changes in the skin itself must be considered. "There may be a greater thickness of the unpigmented epidermis which (unless the epidermis is perfectly transparent) will allow less light of all colors to pass through to the capillary layer, and will, at the same time, scatter more white light back to an observer's eye.

"Without change in the thickness of the unpigmented layer of the epidermis, it may become more milky, so that, as before, less light reaches the capillary layer, while more white light is scattered back to an observer's eye." Finally, "The epidermis may become partially opaque to red light." According to this author, an anemic look may coincide with the very first stage in the production of pigment in the epidermis.

We are aware of striking changes in the structure of the skin in hypothyroidism. The pale, waxy appearance of individuals suffering from myxedema is a striking picture of that disease. This pallor may or may not be associated with changes in the blood. Certainly it is at least partly due to changes in the skin. Is it not possible that a lower metabolic rate with some associated changes in the skin, is another factor in the production of the pale complexion of the South?

There has been considerable discussion regarding the basal metabolic rate in the tropics. On theoretical grounds, "banking the fires," as one writer has put it, would be of considerable value in the acclimatization of persons living in the South. Several workers believe they have demonstrated a low rate. Thus in 47 determinations on 10 white individuals and 10 blacks, de Almeida (3) in Brazil found a distinctly low basal metabolic rate, a finding which he has again confirmed more recently. Montoro (138) in Cuba and Fleming (63) in the Philippines demonstrated a basal rate lower than the accepted standards of New York, while Corlette (34) found similar results in Australia, as did also Sundstroem (200). Hafkesbring and Borgstrom (90) in New Orleans, in a carefully controlled series of 88 experiments on 9 subjects, found the metabolism of individuals living in New Orleans to be definitely lower than the values given by the DuBois, Harris-Benedict, and Dreyer standards, the average deviation from the standard being −18 per cent, −16 per cent, and −14 per cent, respectively. Again, Hindmarsh (100) in Sydney, Australia, found in 76 subjects an average reduction of 10 per cent in men and women as compared with the DuBois predicated values. McConnel et al. (130) found that there is a temperate zone of minimum metabolism between 75° and 83°F. effective temperature and that above or below this temperature metabolic rate is increased.

Not all metabolic studies, however, are in agreement with those above mentioned. Eijkman's (51, 52) experiments in the white and colored race showed a metabolic rate equal to that found in New York. Steggerda and Benedict (196) found in 5 female browns and 8 male blacks in Jamaica a metabolism on the average not markedly different from that of white persons in northern latitudes. Thirty-seven male browns showed a rate of 5.4 per cent below predicted Harris-Benedict values. Williams and Benedict (211) found no change in white members of an expedition to Yucatan, while 32 Mayas had an average rate 5.2 per cent above the standards in New York.

As regards seasonal variation, Gustafson and Benedict, (87) as well as Griffith and his co-workers, have found no differences in metabolic rate at different times of the year, while Gessler (66) reports a seasonal variation.

Differences in diet between hot and colder climates have received the attention of several workers. The studies of Denis, Borgstrom, Hafkesbring, and Bost (38) in New Orleans showed a lower urinary nitrogen output in warm as compared with cold weather. Part of this decreased nitrogen output could be accounted for by loss through perspiration, but protein consumption in New Orleans students also showed a distinctly lower level (60 per cent) as compared with northern standards. Basal metabolic rate appeared to fluctuate with food intake.

Similar results as regards protein consumption in warm countries were found in Sydney, Australia (166). On the other hand, the investigations of several other workers show no similar diminution in food consumption. (50, 169, 5, 69, 29, 200.)

It must be remembered that a metabolic rate lower than that given as normal in northern latitudes, even if finally proven to be general in the South, need not necessarily be the effect of climate. It is not unlikely that the accepted standards are too high. This has been suggested by several investigators recently. Furthermore, more complete relaxation which may be possible in warmer climates may be a factor. The entire subject is still very much unsettled. The influence of a lowered protein intake and basal metabolic rate in the production of "tropical anemia" is thus still a hypothetical, although an interesting one.

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OBSERVATIONS ON THE COURSES OF DIFFERENT TYPES OF BRIGHT'S DISEASE, AND ON THE RESULTANT CHANGES IN RENAL ANATOMY

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[1] The clinic was organized by Dr. Stillman, and with him the general plan of the problem was worked out in its first years. Dr. Möller carried part of the clinical responsibilities during the years 1926–28, and performed the chief part of the difficult task of sifting, ordering, selecting, and charting the accumulated data of former years. Dr. Ehrich has contributed the descriptions of the anatomical changes found in the kidneys at autopsy. Dr. McIntosh carried for five years part of the clinical responsibilities, and assisted in final preparation of the material for publication. Drs. Leiter and MacKay were each associated with the clinic for two years, and Drs. Hannon, Moore, and Johnston for one year. Dr. Moore also assisted in preparing the charts, and Dr. Hannon the text, in the forms finally published.—D. D. V. S.

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The study of nephritis beginning with Bright (1836) has led to the recognition of different types of renal disease which have finally received consistent outlines in the classic monographs of Volhard and Fahr (1914) and Volhard (1918), and the recent work of Addis (1925, 1928). These authors, approaching the problem from considerably different directions, nevertheless agree in the main, and recognize three chief types of nephropathy, of which the outstanding differential characteristics are: (1) Hematuria, acute, intermittent, or chronic, usually with hypertension, and with nitrogen retention, frequent in the acute stage, regular in the advanced chronic stages; (2) marked hypertension, which precedes any serious renal signs; (3) edema and heavy proteinuria without hematuria or hypertension. These three conditions are characterized by Volhard and Fahr as glomerulonephritis, nephrosclerosis ("Nierensklerose"), and nephrosis, respectively; while Addis calls them hemorrhagic, arteriosclerotic, and degenerative Bright's disease.

It was the great service of Volhard and Fahr not only to introduce order and clarity into the clinical classification of nephritides, but also for the first time satisfactorily to relate the clinically defined conditions to anatomical changes in the kidneys. The outstanding and primary histological changes which they observed in the three conditions were respectively: (1) Inflammatory glomerular destruction; (2) thickening of the small renal arteries; and (3) degeneration affecting most markedly the tubules. These were the primary and characteristic changes noted, although the autopsy material yielded by terminal conditions frequently presented in varying degree additional secondary changes. Subsequent observations, including those presented in this paper, have confirmed the essentials, clinical and histological, of Volhard and Fahr's classification.

In this report we present, from a series of cases observed closely over periods varying from weeks to years, objective functional and clinical data, together, in those cases which have come to autopsy, with descriptions of the terminal histology. The data are presented with the hope of adding to the clarity and completeness with which the variable courses of these different types of renal disease can be pictured, and thereby lessening the avoidable error of diagnosis and prognosis.

The object of this contribution is limited by the boundaries of the above statement. Etiology and therapy have been kept constantly in view during the progress of the work, but will enter only incidentally into this presentation.

Nomenclature

With regard to the last two of the three types of renal disease mentioned, there appears to be little difference between the Volhard-Fahr and Addis nomenclatures. "Nephrosclerosis" and "arteriosclerotic Bright's disease" are so nearly equivalent, both in their apparent significance and in the meaning attached to them, that they may be regarded as synonymous, and we have used them as such.

Similarly both Volhard and Fahr, and Addis, speak of the "degenerative" renal diseases. However, the former authors also use nephrosis, as a convenient and familiar synonym; while Addis, in view apparently of confusion that has grown up about the term from controversies concerning the nature of the disease, has abandoned "nephrosis" and uses only "degenerative Bright's disease." We have had somewhat the same feeling, and have to a large extent used the term, "degenerative Bright's disease." We have employed the shorter synonym, however, when the repeated use of the longer one would lead to awkwardness of expression. Doubtless, as Volhard remarks in the introduction to his later monograph (1918), it is more essential to attain clarity concerning the nature of the disease than to be meticulous concerning the etymology of its name.

In the case of the hemorrhagic or glomerular type although there appears to be no difference between Addis and Volhard and Fahr concerning the identity of the disease, there is a difference in the manner in which they have divided it into stages and sub-types. Volhard and Fahr divide the disease into the diffuse and focal forms of glomerulonephritis, which they differentiate chiefly by means of blood pressure, the focal ("herdförmige") nephritis being distinguished by the fact that, from its acute hemorrhagic onset, throughout its course, acute or chronic, the blood pressure remains normal. Likewise Volhard and Fahr appear to consider maintenance of renal function as a characteristic of this type of the disease, except in complicated cases. We have not found it easy to differentiate our cases on the basis of blood pressure, without inconsistency with regard to the renal function. Thus cases 10 and 11 showed decreases of renal function, measured by the blood urea clearance, to 12 and 4 per cent of normal respectively, at minimum points reached 6 and 3 weeks respectively after hemor-

TABLE 1

TYPE OF DISEASE		CLINICAL COURSE	URINE SEDIMENT (ADDIS)	ANATOMICAL CHANGES OF KIDNEYS
Hemorrhagic (glomerulonephritis)		Acute onset. Either heals, improves to a latent condition, or progresses through an intermediate chronic state, usually edematous, with diminishing renal function, to terminate in uremia	Red cells in varying numbers. Blood, epithelial, and granular casts, in all stages except terminal. Hyaline casts in all stages. Broad "renal failure" casts in terminal	*Glomerular inflammation* leading in terminal stage to nearly complete destruction. Intracapillary and extracapillary forms of Fahr. Also varying tubular degeneration and arterial changes
Non-hemorrhagic	Arteriosclerotic (nephrosclerosis)	Insidious onset. Marked hypertension. No edema unless cardiac. Death by cardiac failure, apoplexy or uremia	Chiefly hyaline casts	*Arterioles are diseased,* with contracted lumina, endarteritis, intimal hyperplasia, fatty degeneration, necrosis, in varying degree. Varying proportions of glomeruli destroyed. No marked tubular degeneration. Necrosis of tubules may occur
	Degenerative (nephrosis, lipoid or amyloid)	Insidious onset. Edema, and proteinuria. No hypertension. May end in cure, death by intercurrent infection, or less frequently uremia	Chiefly hyaline casts, few epithelial, fatty, granular, and waxy. No blood casts. Failure casts in cases with terminal uremia. Doubly refracting globules	*Degenerated tubular epithelium.* Varying proportions of glomeruli may be destroyed; hyaline or amyloid. In amyloid type arteriolar walls are more or less infiltrated by amyloid material

rhagic onset: yet neither at any time under observation showed hypertension. Case 18 progressed steadily downwards from the acute through the chronic stage, and is now apparently about to enter the terminal, but has at no time shown hypertension. It has been difficult to conceive that these cases in their renal disease are essentially different from the others in which hypertension, usually transitory, occurred during the first weeks of the acute period.

Addis does not, in his outline of the course of hemorrhagic nephritis, attempt to make a clinical separation of the focal cases. Furthermore his description of the progress of the disease, from the acute onset upwards to cure or to arrest in the latent stage, or downwards through the active chronic to the terminal stage, so precisely fits our observations, that in describing the clinical progress of our cases the use of his terms has been almost unavoidable. We have accordingly used Addis's terminology in the discussion of our observations concerning the course of "hemorrhagic nephritis."

In the discussion of the pathological histology, however, Fahr's anatomical terminology (Volhard and Fahr, 1914) has been followed. One might expect confusion to arise from using one set of terms to indicate conditions in the living cases and another set to outline the anatomical post mortem findings. In fact, however, there appears to be no such confusion: the use of one term to indicate the clinically observed condition and another to express post mortem observations serves the purpose of indicating whether the renal condition under consideration is being discussed on the basis of clinical or anatomical data.

In a semi-diagrammatic and incomplete, condensed form, the more outstanding clinical characteristics of the three main types of renal disease may be represented in table 1 (the synonyms of Volhard and Fahr are enclosed in parentheses).

Details concerning the occurrence of these and other characteristics in each type of renal disease will develop later in the discussion of specific observations covering a group of cases of each type.

CASES PRESENTED

The 67 cases presented have been selected for the most part because they are the ones we have had opportunity to observe most completely.

In addition a few that were under observation for but short periods before death are included for the reason that we obtained autopsies on them.

The cases are grouped as follows with regard to the clinical types of renal disease which they represent and their outcomes. In each group the cases with most favorable outcome, or in which the course of the disease has appeared to be least rapid or severe, have been placed first, while the cases with the most unfavorable or most rapidly fatal outcome have been placed last.

Acute hemorrhagic nephritis. Nos. 1 to 23.

Nos. 1 to 5 inclusive recovered.

Nos. 6 to 16 improved to the latent stage.

Nos. 17 and 18 progressed to the active chronic stage, but still live.

Nos. 19 to 23 progressed to the terminal stage and died in from 3 months to 4 years after the initial acute onset.

Cases admitted in latent form of hemorrhagic nephritis. Nos. 23a and 24.

Both these cases progressed into the terminal condition, one after 4 years and the other after 8 years, in the latent stage. Case 23a still lives but case 24 has died in uremia.

Cases admitted to the active chronic form of hemorrhagic nephritis. Nos. 25 to 37.

Nos. 25 to 30 are progressing but still alive, from 1.5 to 6 years after the first symptoms of their disease appeared.

Nos. 31 to 37 died 2.5 to 12 years after onset of disease.

Terminal stage of hemorrhagic nephritis. Nos. 38 to 50.

All the patients who were in the terminal stage when admitted have died, at periods from 6 months to 13 years after symptoms of nephritis were noticed. In the cases of longest duration there had apparently been latent periods.

Arteriosclerotic nephritis. Nos. 51 to 56.

These patients have all died at periods varying from 3 to 10 years after hypertension was noted. One death appeared to be due to cardiac failure, two were typically uremic, while in the other 3 symptoms of uremia and heart failure were so combined that it was difficult to ascribe exitus more to one than to the other.

Degenerative nephritis or nephrosis. Nos. 57 to 66.

No. 57 made an apparently complete recovery.

Of nos. 58 to 64, 4 are still living, with the disease in an apparently chronic form, and 3 have died from causes other than renal failure.

Nos. 65 and 66 died in typical uremia with nitrogen retention. Of these no. 66 at autopsy was found to be amyloid: autopsy on no. 65 was not permitted.

SIGNIFICANCE OF CLINICAL DATA PRESENTED

In order to present within practicable space observations on so large a series of patients over prolonged periods it is necessary to use graphic methods and limit the data to those of most definite significance. We have accordingly given the results of one functional test, the blood urea clearance, which has proved the most sensitive and reliable. The plasma protein contents have been given as the figures most closely related to the edematous tendency and to the progress of the degenerative type of Bright's disease, hemorrhagic or non-hemorrhagic. The edema itself is represented in a semi-quantitative way, and likewise the proteinuria that, in gross form, is part of the degenerative syndrome. Blood pressure values are given because of their aid in differentiating arteriosclerotic nephritis from the other types, and of their interest in showing something of the incidence of circulatory derangement in hemorrhagic nephritis. Hematuria is shown because of its diagnostic significance in differentiating hemorrhagic from pure degenerative and arteriosclerotic nephritides. Hemoglobin concentrations in the blood are presented because anemia appears to represent one effect of nephritic toxic injury which is measurable, even though it is less serious for the organism than those injuries directly responsible for the uremic syndrome.

The blood urea clearances were determined as described by Möller, McIntosh, and Van Slyke (1928). Each clearance involves urea determinations on one blood sample and on two urine samples passed during successive periods of approximately one hour each.

The plasma proteins were determined by the method of Howe (1921), the globulins being precipitated by 22 per cent sodium sulfate and the albumin determined in the filtrate, all analyses being made by micro Kjeldahl methods.

Hemoglobin concentrations in blood were determined by the method of Palmer (1918).

Proteins in the urine have been determined in a majority of the cases presented by the approximate Esbach method. During the past three years the more nearly quantitative procedure of Shevky and Stafford (1923) has been employed. Because of the semi-quantitative nature of most of the urine protein values we have plotted them in a semi-quantitative manner in the charts.

Hematuria in most of the cases, unless macroscopic, has been determined by the usual microscopic examination of sediment obtained from morning urine. During the past 3 years the quantitative sediment count of Addis (1926), on sediment obtained from urine passed during the last 12 hours of a 24-hour dry diet, has been introduced. Some of the results obtained with it are given in the case histories. Because it was not used in most of the cases presented, we have not designed the charts to indicate millions of cells excreted, but only the relative hematuria roughly differentiated into 4 degrees (see explanation before the charts of the hemorrhagic cases).

Blood pressures have been measured with mercury manometers.

The significances of the above values are discussed below in more detail. The discussion is based in part on the observations of other authors, in part on records presented later in this paper.

BLOOD UREA CLEARANCE

The blood urea clearance is used in our charts as the measure of renal functional ability. That urea retention is characteristic of renal failure leading to clinical uremia has long been recognized. Van Slyke, McIntosh, Möller, Hannon, and Johnston (1930) have presented data showing that the urea excreting ability of the kidneys was, in fact, the most sensitive indicator of the state of the renal function of several which they tested, including blood urea and blood creatinine concentrations, and phenosulfonephthalein excretion. As a measure of the urea excreting power of the kidneys it has been recognized since the work of Ambard (1914) and F. C. McLean (1915 1917) that the most exact information requires comparison of both blood urea concentration and urea excretion in the urine. From the work of Möller, McIntosh, and Van Slyke (1928), it appeared that the simplest and most satisfactory way to express the relationship between these two factors was by means of the "blood urea clearance," by which term they indicated the *cubic centimeters of blood per minute cleared of urea by renal excretion.*

For urine volumes below 2 cc. per minute, as shown previously by Austin, Stillman, and Van Slyke (1921) the blood urea clearance decreases with diminishing urine volume. Diminishing the volume to 1/4 was found to lower the clearance to 1/2: in other words, the clearance varies in proportion to the square root of the urine volume. Making allowance for this influence of urine volume, the blood urea clearance, from determinations with any urine volume below 2 cc. per minute, is estimated for the standard condition that urine volume output is 1 cc. per minute (approximately the normal average output), the formula (Möller, McIntosh, and Van Slyke, 1928) used being:

$$\text{Standard blood urea clearance} = \frac{U}{B}\sqrt{V}$$

where U is the concentration of urea in the urine, B is the concentration in the blood, and V is the volume output of urine in cc. per minute. Van Slyke, McIntosh, Möller, Hannon, and Johnston (1930) found that the relative sensitiveness to renal damage of this clearance was such that it indicated a drop below 40 per cent of normal renal function in a large percentage of progressing nephritic cases when phenosulfonephthalein excretion, blood creatinine, and blood urea considered without its relation to urea excretion, were still within the range of normal variation; and that, in point of time, the blood urea clearance in progressing cases revealed development of functional deficit weeks or months before the other tests above mentioned. Because of the sensitiveness and practicability of the blood urea clearance as a measure of renal function, we have used this one value for the purpose of expressing renal efficiency. In the charts the standard clearance is indicated by the symbol C_s, and is expressed both in cubic centimeters of blood cleared per minute, and in percentages of the average normal clearance, which is 54 cc. per minute for adults. Correction has been made for body size according to the chart for this purpose published by McIntosh, Möller, and Van Slyke (1928), although such correction is important only for children.

For urine volumes above 2 cc. per minute Austin, Stillman, and Van Slyke (1921) showed that the clearance is independent of the volume. With urine volumes over 2 cc. per minute the clearance is calculated simply as $\frac{UV}{B}$. The average value of this "maximum clearance" for normal adults is 75 cc. of blood cleared of urea per minute. Möller, McIntosh, and Van Slyke (1928) in studies on nephritic patients found that with a given subject the same percentages of average normal function are given by the "maximum" blood urea clearance, determined with high urine volume outputs, as by the "standard" blood urea clearance, determined with urine outputs within the usual range. In cases where during the clearance determinations the urine volumes exceeded 2 cc. per minute, we have calculated the maximum clearance in percentage of normal and recorded it as such in the charts. Since urine volumes in hospital patients seldom exceed 2 cc. per minute, unless diuresis is intentionally stimulated, however, nearly all the clearance values shown are "standard clearances."

From a comparison of the terminal clearance values and autopsy findings in cases reported in this paper it appears that in *hemorrhagic and degenerative nephritis one may interpret the blood urea clearance as a measure of the proportion of glomerular tissue still functioning.* In terminal arteriosclerotic nephritis, clearance values which are a small fraction of normal have been found with a large proportion of glomeruli still intact. *It appears probable that in arteriosclerotic nephritis the fall in blood urea clearance is proportional to the decrease in renal blood flow rather than to the glomerular destruction.*

PLASMA PROTEIN CONTENT AND EDEMA

As urea retention in nephritis is the sign of a condition leading to uremia, so is plasma albumin deficit the sign of a condition leading to edema. As, after renal failure, edema is the complication that causes most frequent concern, so is determination of the plasma proteins, after that of the urea excreting ability, the quantitative chemical examination to which we have come to refer most frequently in judging the condition of patients.

In a recent report on results from 75 nephritic patients Moore and Van Slyke (1930) have shown that when the total protein content, normally averaging 7 per cent, falls below 5.2 to 5.8 per cent, or the albumin, normally averaging 4.3 per cent, falls below 2.3 to 2.7 percent, or the plasma specific gravity, normally averaging 1.027 falls below 1.0225 to 1.0235, edema is usually present. The figure most closely connected with the edematous tendency appears to be the albumin, but as the globulin usually remains unaffected, the total proteins and the specific gravity, which reflects the total proteins, as a rule both parallel the albumin and show the same correlation with edema.

While urea retention is a warning, and not in itself apparently the cause of uremia, there is fair proof that plasma protein deficit is an important direct cause of non-cardiac nephritic edema.

Evidence that plasma protein deficit predisposes to edema was first given by the physiological experiments of Starling (1895–96). He measured the osmotic pressure of the plasma proteins and found it at a level of about 30 mm., between arterial and venous blood pressures. Starling pointed out that it is presumably this osmotic attraction of the plasma proteins for water that balances in the capillaries the hydraulic pressure tending to force the fluid out into the tissue spaces, and that when the protein osmotic pressure weakens, because of decrease in protein concentration, undue amounts of fluid are likely to pass out into the tissues. He found that the edematous leg of a dog perfused with Ringer's solution remained edematous, but when perfused with serum the edema fluid was reabsorbed. The salts present, although in molar concentration many times exceeding the proteins, have relatively little effect in controlling fluid diffusion because the salts themselves diffuse freely through the capillary walls.

That proteins are scant in the plasma of many nephritic patients was noted by Bright (1836). Csatary (1891) noted that the deficiency affected the serum albumin more than it did the globulin, so that the albumin: globulin ratio, normally 1.5 to 2.0, frequently fell below 1 in nephritis. These observations have been confirmed and amplified by other authors, whose work has been reviewed by Linder, Lundsgaard, and Van Slyke (1924). It was Epstein (1917), however, who connected the observation of plasma protein deficit with Starling's experimental and theoretical work to form an explanation of the cause of non-cardiac edema in nephritis. This explanation, viz., that the decreased osmotic attraction of the proteins for water permits the escape of the latter into the tissues, has been confirmed by the work of Govaerts (1924), of Schade and Claussen (1924) and of Cope (1928) who determined directly the osmotic pressure in the sera of normal subjects and of nephritic patients with and without edema.

As might be expected, the relation between protein deficit and edema formation is not an entirely regular and uniform one. There are other factors which resist or reënforce the hydropigenous effect of plasma protein deficit. With plasma proteins near the level at which their deficit usually produces edema, the latter may be present or not, and may come and go in the same subject, as these other modifying factors exert their influence in one direction or the other. Salt intake is such an influence: a patient with fairly low plasma protein content and edema may lose the latter merely by being put on a salt free régime, although, as Moore and Van Slyke (1930) have shown, entire disappearance of edema is infrequent if the proteins are below the above quoted critical levels. There are other less tangible influences. In a patient with tendency to edema barely under control edema may appear after infections or operations, and disappear during recovery. In some instances fever appears to tend to make edema disappear; in others vomiting shows a desiccating effect. And in some cases on the border line edema comes and goes for no observable reason.

In the first weeks of acute nephritis edema may occur with plasma protein level normal; this edema is due to some influence quite apart from the osmotic effect of the plasma proteins; it may arise from some toxic effect increasing capillary permeability. Again in the terminal stage of hemorrhagic or arteriosclerotic nephritis edema may occur as the result of heart failure.

With these exceptions, the accumulated data indicate that the constant and dominating factor in producing non-cardiac edema in Bright's disease is plasma albumin deficit, the effect of which is only modified in degree by other influences, and that Epstein's application of Starling's theory has been justified by the studies of subsequent investigators. The data presented in the charts of this monograph provide further support for the above statement, at the same time that they furnish examples of the effects of other influences in modifying that of plasma protein deficit.

The fact that tendency to edema formation is closely related to plasma albumin deficit and relatively unaffected by globulin changes is explained by Govaerts' (1924) finding that the albumin exerts four times as much osmotic pressure per gram as the globulin.

PROTEINURIA

Since proteinuria was shown by Bright to accompany renal disease it has maintained its place as a sign of primary diagnostic importance. To its original significance as an evidence of renal injury recent years have added another. Heavy protein excretion in the urine is accompanied in almost all cases by protein deficit in the blood plasma, and there is a rough parallelism between the two. As indicated by the observations of Linder, Lundsgaard, and Van Slyke (1924), loss of albumin in the urine does not appear to be the sole cause of albumin deficit in the blood plasma. The malnutrition common in the edematous types of nephritis adds its effect, apparently by retarding regeneration of albumin. In a rough approximate way, however, the magnitude of protein excretion corresponds with the degree of protein deficit in the blood plasma. Both gross proteinuria and plasma protein deficit are the almost regular accompaniments of the degenerative types of renal disease, hemorrhagic and non-hemorrhagic. The protein that appears in the urine in these types of nephritis (except the amyloid) is 85 per cent or more albumin, relatively little globulin being excreted in the urine or missing from the plasma (for data and literature see Hiller, McIntosh, and Van Slyke, 1927). Correspondingly, as mentioned above, the protein loss in the plasma is as a rule confined to the albumin fraction.

It is in the degenerative types that the urinary protein output has the greatest interest, but in all types it assists in the diagnosis, the scanty output in the sclerotic type helping with the hypertension to differentiate the condition from the degenerative and hemorrhagic, or, in the terms of Volhard and Fahr (1914), from the nephrotic and glomerular types of renal disease.

HEMATURIA

Gross hematuria has long been recognized as a common sign of acute, and microscopic hematuria as one of chronic, glomerular nephritis (Volhard and Fahr, 1914). Addis (1925) points out that of all the clinically observable abnormalities of glomerular nephritis, hematuria determined under standardized conditions, is the one which is most characteristic and of most assistance in differentiating the condition from the pure degenerative (nephrosis) and arteriosclerotic types. In order to obtain as nearly as possible a quantitative measure of hematuria Addis puts his patients for 24 hours on a dry diet and centrifugates the urine passed during the last 12 hours. Thus a concentrated urine is usually obtained in which the red cells do not dissolve. The latter are counted in the sediment. In part of our cases Addis' sediment counts have been made and are recorded in the case histories. Unfortunately most of the observations reported in this paper were made before Addis' procedure was introduced into our clinic. The results shown, even by the less precise ordinary microscopic procedure, however, go far to confirm the importance that Addis attaches to hematuria as a diagnostic sign of hemorrhagic or glomerular nephritis. In the acute and terminal stages of the disease hematuria, macroscopic or readily detectible by ordinary microscopic observation, has been constant. During the active chronic stage hematuria has usually been constant, sometimes intermittent, as determined by ordinary examination. Since the introduction of the Addis sediment count microscopic hematuria in excess of normal has been found to be practically constant in the active chronic stage. The one phase of the "hemorrhagic" disease which is not hemorrhagic is encountered during inprovement or recovery from the acute disease. The hematuria may completely disappear while there is still heavy proteinuria, albumin deficit in the plasma, and some tendency to edema. There follows then a period of some weeks or months during which such a case is indistinguishable, except for its history, from a pure nephrosis. With this exception it appears that some degree of hematuria is nearly constant throughout all stages of the condition which Volhard anf Fahr call glomerular nephritis and Addis terms hemorrhagic Bright's disease. That hematuria may also occur in the terminal collapse of what Volhard and Fahr term the malignant type of nephrosclerosis does not detract seriously from its value as a diagnostic characteristic.

ANEMIA

Brown and Roth (1922) have reviewed the literature concerning anemia in nephritis, and have presented data indicating that the anemia is due to injury of the bone marrow, which tissue shares in the constitutional damage that is known to be suffered by the heart, retina, and blood vessels. Brown and Roth (1922, 1923) further presented figures showing a definite prognostic significance of anemia in nephritis. In a group of 139 cases, those with no anemia showed in 2.5 years 18 per cent mortality. Those with 60 to 85 per cent of normal hemoglobin content showed 46 per cent, and those with less than 60 per cent of normal hemoglobin showed 85 per cent.

BLOOD PRESSURE

Hypertension is the quantitatively measurable effect of circulatory change in nephritis. The literature up to 1913 has been summarized by Janeway (1912–13). The conclusions concerning the relation of hypertension to the different types of renal disease reached from his own observation by Janeway can still be quoted unamended. They are as follows. We have changed only the order, and prefixed to the conclusion concerning each condition the name given that condition in the terminology now used.

1. *Hemorrhagic nephritis* (*glomerular nephritis*). "Hypertension may arise in connection with the unknown intoxication which causes disturbances in the central nervous system and which we call uremia. . . . . Clinically this intoxication is associated with severe acute nephritis, sometimes at its very onset, besides the subacute and chronic inflammatory affections of the kidney."
2. *Arteriosclerotic nephritis* (*nephrosclerosis*). "Hypertension may arise in primary irritability of the vasoconstricting mechanism from unknown, probably extrarenal, causes, which lead eventually to arteriolar sclerosis. In this type the disease of the kidney is the sequence, not the cause, of the generalized vascular lesion. When it progresses to a condition of extreme atrophy, resulting in the true primary contracted kidney, a renal element may be added to the existing hypertension."

According to Janeway's conception the hypertension of hemorrhagic nephritis is a result of the renal disease, while that of arteriosclerotic type precedes the renal disease. In this conception Volhard and Fahr (1914) concur. Branch and Linder (1926) in autopsies of 7 cases of typical terminal hemorrhagic nephritic deaths, preceded by periods of nitrogen retention and hypertension, found in one case no arterial changes. Their findings support Janeway's conclusions.

SUMMARY OF CHIEF SIGNIFICANCES OF DATA CHARTED

The apparent significance of the different values we have charted may be summarized as follows.

Blood urea clearance. Measure of intact glomeruli in hemorrhagic and degenerative cases, of renal circulation in arteriosclerotic cases.

Hematuria. Sign of active inflammation in glomeruli.

Hypertension. Sign of circulatory changes. When high and prolonged indicates anatomical changes in small arteries.

Plasma protein deficit. *Gross proteinuria.* *Edema.*	Signs of degenerative syndrome. Accompany degenerative renal changes, with or without glomerular damage.

Anemia. One of the indications of toxic damage to organism.

Edema, besides accompanying the degenerative syndrome, also occurs, as mentioned above, in the initial weeks of acute hemorrhagic nephritis, and in the cardiac failure that frequently forms part of the terminal failure.

UNCHARTED DATA

Besides the data above listed, and recorded on the graphic charts, we have, either continuously or at stages during the ten years which these studies cover, made observations of most of the other signs and functional measurements which, according to the current literature, have given promise of throwing light on the conditions of the patients.

As measures of renal function the concentration and dilution test was carried on for several years, and the phenolsulfonephthalein excretion test of Rowntree and Geraghty (1910) has been carried out parallel with the blood urea clearance throughout the course of these studies. The concentration and dilution test is so subject to the influence of water retention and elimination by edematous patients, and to the influence of variations in the salt content of the diet, that it is less reliable than the blood urea clearance. The phthalein excretion, as stated above in the discussion of the blood urea clearance, has been found markedly less sensitive than the latter as an indicator of renal deficit. The phthalein showed one point of special interest; occasionally when an acute case, after suffering marked functional loss, began to improve, the phthalein would begin to rise some time before the blood urea clearance. We at first attempted to include the phthalein values in the charts, but under the necessity for condensation, and in view of the fact that except for the above point the phthalein shows less about renal function changes than does the clearance, we felt forced to eliminate the former.

The blood urea content, when taken without relation to the urea excretion, may, as shown by Van Slyke, McIntosh, Möller, Hannon, and Johnston (1930), like the phthalein excretion, fail to show a definite abnormality until the renal function, as measured by the blood urea clearance, has fallen to 20 per cent of normal. The same was found true of the blood creatinine content. For comparison with other data of the same sort in the literature some of the blood urea and creatinine values are given in the histories, but there was obviously no object in charting them.

Plasma fats and cholesterol have been followed in a large proportion of our cases because of the concurrence of lipemia and hypercholesterolemia with nephrosis. Plasma protein contents, however, are determinable by more accurate methods, and plasma protein deficit appears to be as closely related to the nephrotic syndrome, and more directly related to the edema, than the lipoids, hence we have not reported the latter.

The ions of the plasma, K^+, Na^+, $Cl' \cdot HCO'_3$, and H^+, show variations of great interest, especially in the terminal stage of renal failure, as shown by Austin, Peters, and their collaborators (Sunderman, Austin, and Camack, 1928; Bulger, Peters, Eisenmann, and Lee, 1926), and plasma electrolytes have been studied in our patients. However, the relationship of plasma electrolyte changes to renal failure and edema are less constant and definite than are the relationships of the urea excreting power and plasma albumin content, respectively, to these nephritic results. The interesting details of mineral metabolism have furthermore appeared incapable of treatment within the limits of the present monograph.

The basal metabolism has been determined in nearly all cases, and some of the results are given in the abstracts of case histories. The basal metabolic rates were chiefly of use in guiding treatment with thyroid substance or thyroxin in the degenerative cases, in a minority of which such treatment appeared to give beneficial results in assisting the elimination of edema.

Counts of the formed elements in the sediment of the concentrated urine voided during the last 12 hours of a 24 hour dry diet have been carried out *by the method of Addis* (1925) on patients admitted during the past 3 years. Since, however, they are lacking in the majority of cases, these counts are not charted. In cases where they are available some of the counts are given in the case history abstracts. The normal variations in the 12-hour output of the formed elements, according to an examination of 74 students by Addis (1926) are: casts, 0 to 4200; red cells, 0 to 425,000; white blood and epithelial cells, 32,000 to 1,800,000. The normal casts are all of the hyaline variety, without any fat droplets.

PLAN OF PRESENTATION OF DATA

In the following pages we shall, for each of the three main types of nephropathy, give an outline of the general course of the disease, followed by a discussion of the specific changes noted as illustrated in our charts, by a discussion of the anatomical changes found at autopsy, and finally by abstracts of the histories of the charted cases, together with individual autopsy reports.

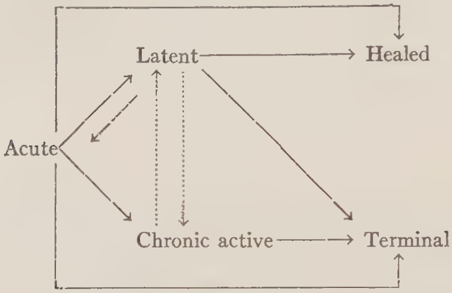
The introductory outline of the course of each disease is intended chiefly to identify, independently of the nomenclature used, the type of nephropathy concerning which specific data are presented in the subsequent section, and to indicate the nature of these data sufficiently to assist the reader in orienting himself with regard to them at the outset of their subsequent detailed discussion. The outlines are therefore brief, and in them we have made no attempt to review the literature or to present detailed clinical descriptions. These can be found in the works of Volhard and Fahr (1914) and Volhard (1918). The latter author is furthermore engaged in the preparation of a new monograph on the subject (personal communication), to which, perhaps the chemical, functional, and anatomical observations in our paper may serve as a useful supplement.

Hemorrhagic or Glomerular Nephritis

GENERAL COURSE OF THE DISEASE

Addis has pictured the course of the disease by a diagram which, with slight changes,[2] is the following:

Hemorrhagic nephritis



The more usual changes are indicated by arrows with unbroken shafts. The dashed arrow indicating change from chronic active to latent stage represents a favorable outcome of the chronic active which is so rare that the writers have only once observed it. Addis, however, has seen it several times (personal communication). The reversed arrow leading backwards from the latent to the acute indicates an exacerbation occurring after progress towards healing has reached the latent stage. Less frequently, an exacerbation may cause a change from the latent to the chronic active stage.

In the progress of the disease the different stages are, of course, not sharply marked off from one another. It is usually impossible to state that within a certain week the acute stage changed definitely

[2] In Addis' original paper (1925) the first stage of the disease was called "initial" instead of "acute." However, the condition produced by an exacerbation of a latent case is frequently identical in symptoms and outcome with that of a fresh, acute case. The exacerbated case resembles the fresh one in hematuria, edema, relatively rapid variability, and chance of improving to the latent condition, a chance which, according to the writers' experience, is almost nil in the chronic active stage. Since it would be inaccurate to call an exacerbated case "initial," we have retained the term "acute" to cover both initial and exacerbated cases. Otherwise we have followed Addis.

The authors have enjoyed the benefit of Addis' personal discussion and criticism of part of the following portions of this paper, and for this advantage are greatly in his debt.

to the latent, or passed into the chronic active. Likewise the boundary between the chronic active and terminal stages is broad and hazy. The transition periods, during which the disease is passing from a condition frankly belonging to one stage to that belonging clearly to the next may cover weeks, or even months. Nevertheless the disease in its progress does pass through periods clinically so different that they have at times been defined as different entities, and the convenience of using concise characteristic names to define these stages appears to justify a differentiating nomenclature.

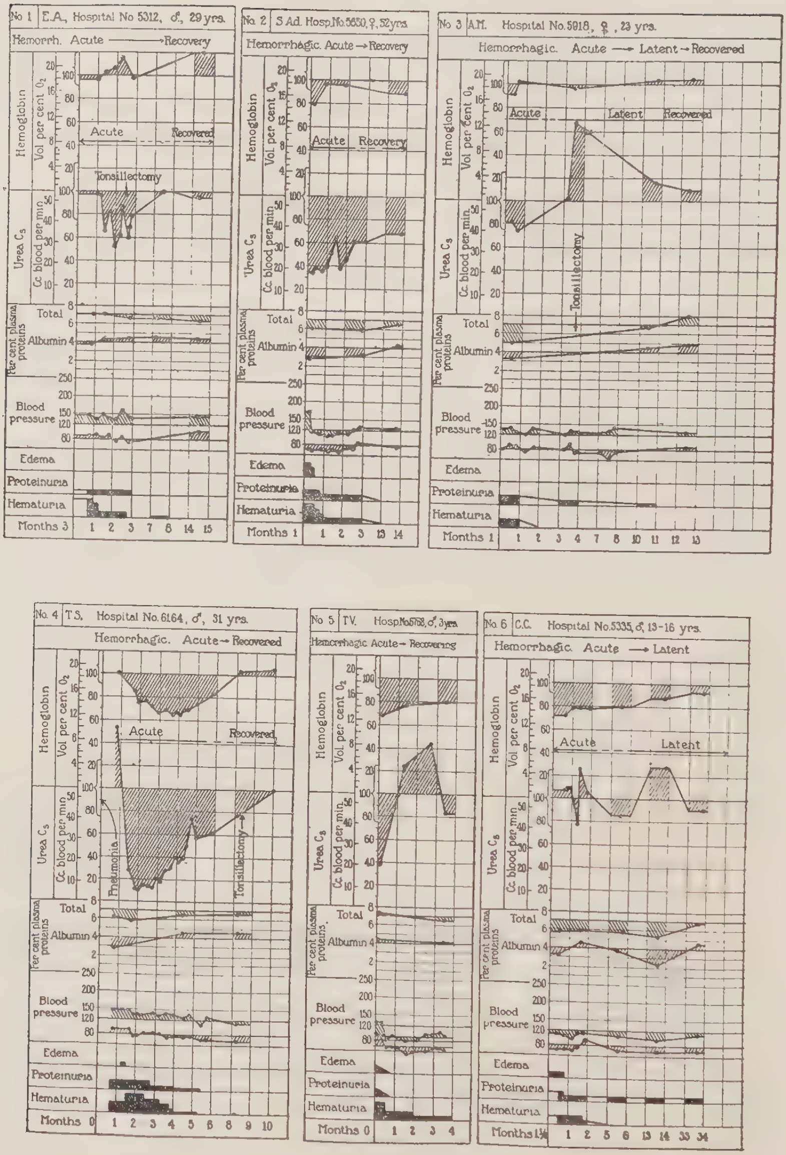
Acute hemorrhagic nephritis (cases 1 to 23)

The acute stage with its sudden onset is familiar. It is marked regularly by hematuria, proteinuria, and edema, while diminution of renal function, hypertension, plasma protein deficit, and some anemia are frequent. Opinion seems to be coming to a general agreement that the cause is nearly always some type of streptococcus infection (Volhard and Fahr, 1914; Addis, 1925; Longcope and collaborators, 1927).

From the severity or the mildness of any of these symptoms, except plasma albumin deficit, during the first weeks of the acute stage it is, according to our data, impossible to predict whether the outcome is likely to be favorable or unfavorable.

The acute stage may have any one of four outcomes. (1) The patient may completely recover, without any detectible sign of the disease remaining (cases 1 to 5). (2) He may improve and become free from subjective symptoms of the disease, but retain some albuminuria, hematuria, or diminution in renal function, the disease becoming latent (cases 6 to 16). (3) The disease may progress into the active chronic form, almost always with subsequent more or less gradual progress to the terminal stage (cases 17, 18, and 20). (4) The disease may hasten in a few weeks directly from the acute to the terminal stage, and in a few months terminate in uremia (cases 21, 22, and 23).

The duration of the acute stage, in our cases which recovered or improved to the latent state, varied from 4 to 15 months. Noticeable improvement *began* within 4 months, in all cases that were not destined to pass into the chronic or terminal stages. In the cases which recovered most slowly (nos. 13 and 16) the last subjective symptom to disappear was the tendency to edema formation. The last clinical


No 1 E.A., Hospital No 5312, ♂, 29 yrs.
Hemorrh. Acute → Recovery
Tonsillectomy
No 2 S Ad. Hosp.No.5650, ♀, 52yrs.
Hemorrhagic. Acute → Recovery
No 3 A.M. Hospital No. 5918, ♀, 23 yrs.
Hemorrhagic. Acute → Latent → Recovered
Tonsillectomy
No. 4 T.S. Hospital No. 6164, ♂, 31 yrs.
Hemorrhagic. Acute → Recovered
Pneumonia
Tonsillectomy
No 5 T.V. Hosp.No.5768, ♂, 3 yrs.
Hemorrhagic Acute → Recovering
No 6 C.C. Hospital No.5335, ♂, 13-16 yrs.
Hemorrhagic. Acute → Latent
Hemoglobin
Vol per cent O₂
Acute
Latent
Recovered
Recovery
Urea C₈
Cc blood per min
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months

CHARTS 1–6

sign to disappear was usually the proteinuria, which frequently persisted for months after the patients were subjectively well, and after hematuria could no longer be detected by ordinary microscopic oxamination (cases, 3, 6, 7, 9, 13, 15 and 16). Sometimes, however, microscopic hematuria has been noted as the most persistent sign.

Latent hemorrhagic nephritis (Cases 6 to 16, 23a, 24 and 31)

After the acute stage has lasted for a period of 2 to 4 months, unless the patient is fated to pass into the chronic or terminal condition, he begins to improve, and makes either a complete recovery, or a partial one to the latent condition, in which he is subjectively well, but in which more or less albuminuria, or slight hematuria, or a subnormal blood urea clearance, indicates that renal conditions are not quite restored to normal. Usually the blood pressure is now normal, but in an occasional case some hypertension may remain (case 12). In some cases the nephropathic signs eventually disappear, and recovery is apparently complete (case 10). Other cases may remain in the latent state for years, and eventually, sometimes as the result of an exacerbation due to infection (Addis, 1928), at other times for no tangible reason, may resume progress towards renal failure, and terminate in uremia. In cases 23a and 24 a slow fall in blood urea clearance set in after latent periods of 4 and 7 years respectively, and has already led to uremic death in case 24.

Rarely a patient reaches a latent condition as the result of arrested progress after the disease has reached the active chronic stage, sufficient renal function being maintained to permit ordinary activities. The only such case in our series is no. 31. The usual case which enters the active chronic stage passes more or less steadily downwards to the terminal.

Active chronic hemorrhagic nephritis (cases 17, 18, 20 and 25 to 37)

This corresponds in most cases to Volhard and Fahr's nephrotic type of glomerulonephritis, and to hemorrhagic chronic parenchymatous nephritis in the older American terminology.

For use in this paper we define the condition as hemorrhagic nephritis that has become chronic, with diminished urea excreting power and signs of active progress, but with blood urea clearance still above 20 per cent of normal. (For reasons stated below, we classify chronic cases with lower clearances as terminal.)

Within a period that in our cases does not exceed 4 months from the acute hemorrhagic onset, unless improvement begins the disease enters either the terminal stage, or more frequently what Addis (1925) calls the active chronic stage. The subject remains ill, malnourished, and unless under strict regime, usually edematous. Hematuria continues, but sometimes at so diminished an intensity that the red cells are detectible only microscopically by Addis' (1925, 1928) special method of examining by quantitative count the sediment of urine passed during the last 12 hours of a 24 hour dry diet. From whatever level it has emerged from the acute stage of the disease, the renal function, as measured by the blood urea clearance, maintains a progress which, observed over periods of months, usually tends steadily downwards. At best it may remain stationary for some months. In this stage improvement to the latent condition may occur, but such improvement is rare. Addis (personal communication) states that he has seen a few cases. In our series there is but one, no. 31.

The active chronic stage is usually accompanied by all the signs, described later, of degenerative renal disease, marked proteinuria, low plasma albumin and total protein content, high plasma fat and cholesterol contents, tendency to edema formation, and by the occurrence (Addis, 1925), from degenerated tubules, of epithelial cells and casts in the urine. The relationship between edema and plasma albumin deficit is that quoted above in the discussion of the significance of plasma protein content, and is the same as in nephrosis.

The differential diagnosis between this stage of hemorrhagic nephritis and the pure non-hemorrhagic degenerative Bright's disease (nephrosis) is not always easy. The active chronic stage of hemorrhagic nephritis, because of its preponderating degenerative element usually has every sign and metabolic abnormality of nephrosis. Both conditions, as Addis points out (1928) represent degenerative renal disease, the difference being that the hemorrhagic type has an additional pathological factor. This factor has been shown by Volhard and Fahr to be glomerular inflammation. The symptoms that have been used to distinguish the hemorrhagic (or glomerular) disease from pure nephrosis have been the presence of hypertension and nitrogen retention (Volhard and Fahr) and of hematuria (Addis). Hypertension, however, is absent in some cases of chronic hemorrhagic nephritis. Nitrogen retention in the chronic active hemorrhagic disease may be only relative and capable of detection when blood and urine urea contents are compared by means of the blood urea clearance determination. Also, nitrogen retention sometimes occurs in the later stages of pure degenerative renal disease, as will be shown later. Microscopic hematuria, usually constant in the hemorrhagic disease, sometimes intermittent, appears to be the most consistent single differential sign. After hematuria, hypertension appears to be the most valuable diagnostic sign. If present it may generally be accepted as ruling out nephrosis. The history often helps. History of an acute onset with hematuria is sufficient to indicate that the observed condition is a phase of the hemorrhagic or glomerular disease.

The justification for separating degenerative cases into hemorrhagic and non-hemorrhagic lies in the different prognoses. The hemorrhagic degenerative disease, once become chronic, almost regularly runs into the terminal stage described below, and uremia. The pure non-hemorrhagic degenerative disease may likewise lead to uremia, but it is more likely to continue without renal failure, and to terminate either by recovery or (more frequently in our experience) by death from intercurrent infection, either streptococcus or pneumococcus.

Chronologically the active chronic stage of hemorrhagic nephritis is intermediate between the acute and terminal stages, and usually covers a period of from 6 months to 2 years. Death usually occurs in less than 3 years after the active chronic stage is reached. We have had, however, 2 cases (nos. 21 and 31) out of 20 survive for 5 years.

Some rapidly progressing cases pass so quickly from acute to terminal that there is no intermediate stage (e.g., cases 19 and 21 of our series).

Terminal hemorrhagic nephritis (Cases 19 to 24 and 27 to 50)

With the progress of the disease the picture eventually changes from that outlined above for the active chronic stage, and assumes that of the terminal. Renal function, measured by the blood urea clearance, becomes stabilized at a lower level, and no longer shows occasional upward fluctuations. Henceforth it moves but little except for its gradual or rapid decline. The signs of degenerative disease, viz., non-cardiac edema, albuminuria, epithelial casts and cells in urinary sediment, low plasma albumin content, may continue undiminished to the uremic end, but they usually diminish and often disappear. *The picture of the uremic syndrome tends to replace that of "wet nephritis." Since the general change appears to come when the blood urea clearance has settled steadily below 20 per cent of normal, we have used that point as an arbitrary boundary between the active chronic and terminal stages.*

With the rise of plasma albumin which frequently occurs during progress into the terminal stage, the tendency to edema diminishes; when the albumin content exceeds 2.5 per cent the tendency to edema may nearly or quite disappear. At such a time the patient, because rid of the annoyance of the edema, is likely to feel subjectively improved. The renal function, even though it has fallen to 20 per cent of normal, may still be adequate to maintain freedom from toxic retention symptoms. In fact the urea and creatinine contents of the blood may remain for some time but little above the upper normal limits (Van Slyke, McIntosh, Möller, Hannon, and Johnston, 1930). This period constitutes the pre-uremic interval of the terminal stage. It may last as long as 2 years (cases 27 and 29).

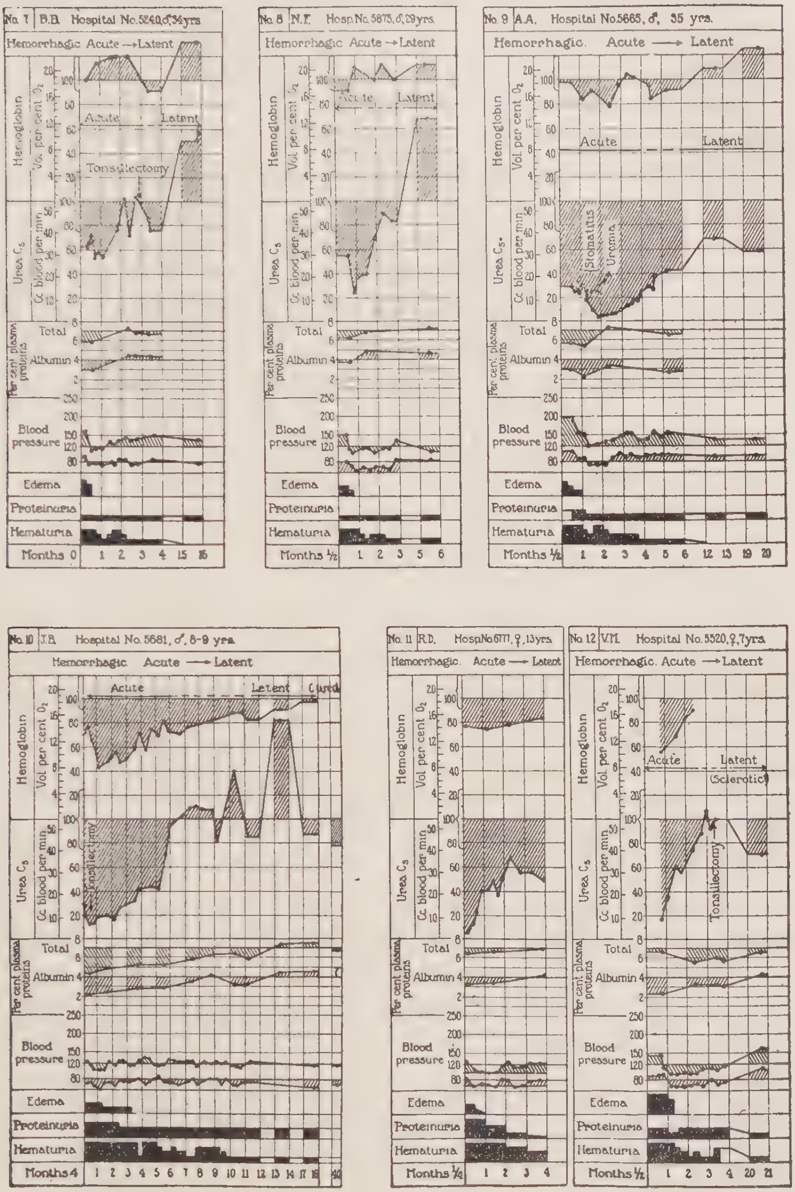
When the renal function does change, however, it falls, often rapidly. Gross retention of urea, creatinine, and phosphoric acid ensues and uremia sets in, unless the latter is preceded by cardiac failure.

The duration of the disease, from the time when the blood urea clearance sank permanently below 20 per cent of normal, in the majority of our cases in which we could measure the interval, has been less than 1 year (nos. 20, 21, 22, 23, 24, 31, 32, 35, 36 and 37). In a minority it has been between one and two years (nos. 27, 29, 34, 44 and 46), and in only two has it exceeded two years (nos. 19 and 38).

EXPLANATION OF CHARTS

For the hemoglobin values two scales are given. The scale to the left gives cubic centimeters of oxygen bound by the hemoglobin in 100 cc. of blood, the "volumes per cent O_2" scale. The scale to the right gives per cent of Haldane's mean normal hemoglobin value, which is equivalent to an oxygen capacity of 18.5 volumes per cent O_2.

For the standard blood urea clearance, C_s, two scales are also given.


No. 7 B.B. Hospital No. 5240, ♂, 34 yrs
Hemorrhagic Acute → Latent
Acute
Latent
Tonsillectomy
Months 0 1 2 3 4 15 16
No. 8 N.F. Hosp. No. 5875, ♂, 29 yrs.
Hemorrhagic Acute → Latent
Acute
Latent
Months ½ 1 2 3 5 6
No. 9 A.A. Hospital No. 5665, ♂, 35 yrs.
Hemorrhagic. Acute → Latent
Acute
Latent
Stomatitis
Uremia
Months ½ 1 2 3 4 5 6 12 13 19 20
No. 10 J.B. Hospital No. 5681, ♂, 8-9 yrs.
Hemorrhagic. Acute → Latent
Acute
Latent
Cured
Tonsillectomy
Months ¼ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 17 18 40
No. 11 R.D. Hosp. No. 6177, ♀, 13 yrs.
Hemorrhagic. Acute → Latent
Months ½ 1 2 3 4
No. 12 V.M. Hospital No. 5520, ♀, 7 yrs.
Hemorrhagic. Acute → Latent
Acute
Latent (Sclerotic)
Tonsillectomy
Months ½ 1 2 3 4 20 21
Hemoglobin
Vol. per cent O₂
Urea Cs
Cc. blood per min.
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria

CHARTS 7–12

The scale to the left shows cubic centimeter of blood cleared of urea per minute by the kidneys. The scale to the right shows the clearance values in per cent of the normal mean, which is 54 cc. per minute (Möller, McIntosh, and Van Slyke, 1928).

The plasma protein scales are obvious.

The blood pressures are given in 2 curves, the upper representing systolic, and the lower diastolic pressure, in millimeters of mercury.

For each of the above 4 values the mean normal is represented by a heavy base line. The shaded space between this line and the broken line indicating observed values shows the deviation of the latter from the average normal. When the shaded area extends downwards from the base line the observed value is below the normal average, and *vice versa.*

The vertical spaces which are left unshaded indicate periods during which no observations were made, usually because the patient was out of the hospital.

At the bottom of each chart are spaces indicating in a semi-quantitative way the amounts of edema, albuminuria, and hematuria. The black areas have the following significances.

HEIGHT OF BLACK AREA IN FIFTHS OF TOTAL SPACE	EDEMA	PROTEINURIA PER 24 HOURS	HEMATURIA
		grams	
1	Trace	Under 1	Slight microscopic
2	Moderate pitting	1 to 4	Marked microscopic
3	Marked pitting edema	Up to 10	Slight macroscopic
4	General edema with ascites	Over 10	Marked macroscopic

In each case for which autopsy data are presented with the case history, "Aut" is marked near the right hand margin of the chart.

At the bottom of each chart the number at the left nearest "months" indicates the number of months the disease was noted before the patient entered the hospital. The other numbers in the bottom row indicate months after first admission.

Charts of cases 1 to 50 inclusive.

CLINICAL OBSERVATIONS IN CASES OF HEMORRHAGIC NEPHRITIS (CASES 1 TO 50)

Urea excreting power in hemorrhagic nephritis

Of the 23 cases observed in the *acute period* all except nos. 3, 6, 18 and 20 showed during the first two months after onset a *fall of the blood urea clearance* to 50 per cent or less of normal. Remembering that the cases are ranked in order according to the gravity of their outcome, we can not conclude that maintenance of normal renal function during the first months of the acute stage justifies either a good or bad prognosis. Cases 3, 6, 18 and 20 maintained normal function during the acute stage. Of these, case 3 made an apparently complete recovery, 6 improved to the latent stage, with prospects for recovery, while 18 and 20 steadily progressed into the chronic condition, with increasing loss of function; case 20 has already died in uremia and there is no ground to hope better for 18.

Nor does it appear that we can attach prognostic significance to the *degree* of functional impairment shown during the first two months. In case 4 within two weeks of onset the clearance fell to 10 per cent of normal, yet an apparently complete recovery was made. In case 9 the clearance two and one-half months after onset fell to 4 per cent, with uremic symptoms, and was followed by recovery to at least as far as the latent condition.

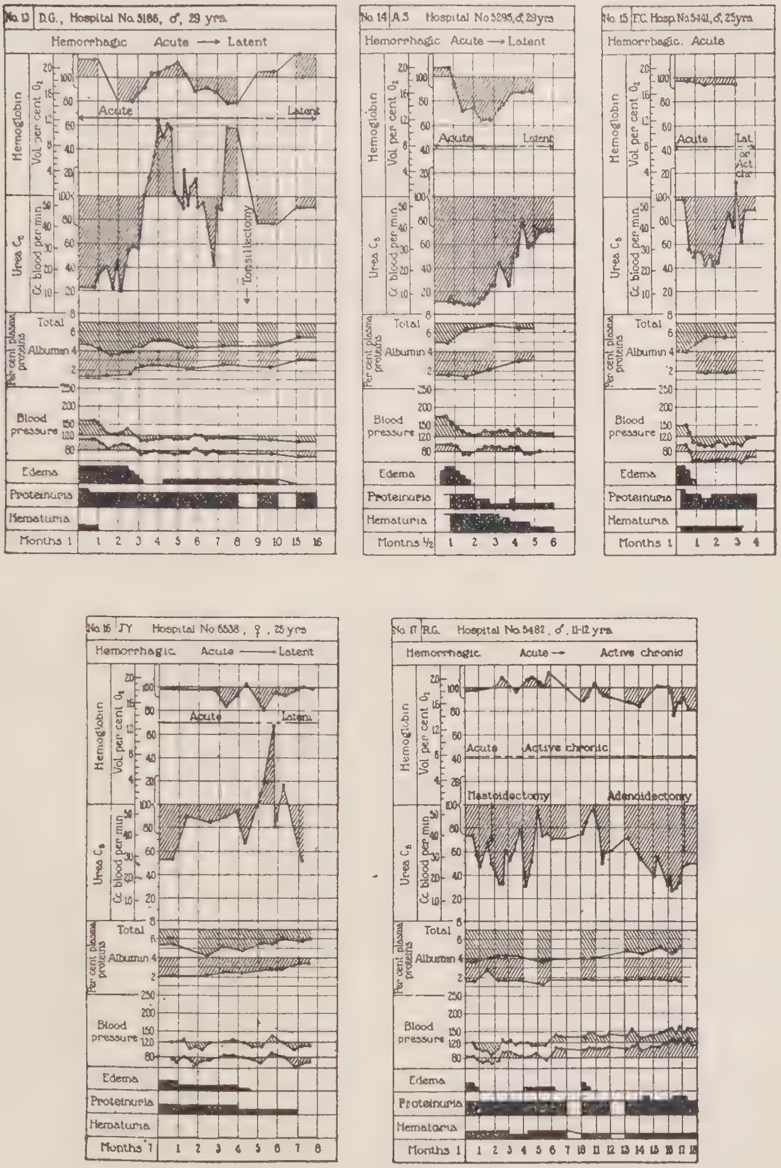
The essential for a good prognosis is that within 4 months after the acute onset the clearance, if it has fallen, shall have begun a consistent climb back towards a normal level. In all of our cases that have recovered or improved to the latent condition the clearance has either remained normal or has begun to rise within this time.

The functional recovery is not always complete. In cases 9 and 11 recovery was subjectively so complete that the patients left the hospital although their clearances had reached only 50 to 60 per cent of average normal. Considering that an occasional healthy person may show clearances as low as 70 per cent of the average, however, 50 to 60 per cent indicates a satisfactory function if maintained. We have not had an opportunity to observe a latent case with such function long enough to ascertain whether the partial functional deficit was permanent, but Addis (personal communication) has seen cases in which it was so, the patients remaining stabilized, subjectively well, with only part of normal function. In such cases it appears probable that some of the glomerular damage of the acute stage has become permanent, but that a large proportion of the glomeruli have recovered, and that they may remain intact for considerable, perhaps indefinite, periods.

In all cases in which marked fall of blood urea clearance occurred during the initial months, and no definite tendency to rise followed within four months after onset, progress downwards to the active chronic or terminal stage followed (cases 18 to 23). In one case (17) such progress occurred even after a temporary return of the clearance to the normal range. In this case there was continuous active infection, necessitating two operations, one for mastoiditis and one for the removal of adenoids.

In the *chronic active period of hemorrhagic nephritis* the blood urea clearances in our cases (nos. 17 to 37) tell a single melancholy tale. The function changes are ultimately all for the worse. There may be periods of several months or even more than a year when progress is arrested. In case 31 alone was the stay sufficiently prolonged and definite to constitute an obviously latent period in the disease. This case, a boy of 6, some months after tonsillectomy was subjectively and clinically so improved that he was discharged, although his urea clearance was only 25 per cent of normal. During the next four years he lived a fairly normal life, and his clearance rose to 40 per cent normal. Then, however it fell in some months to 10 per cent and uremia followed shortly. In all our other cases the disease has shown much shorter hesitations in its march towards terminal uremia.

In the *terminal stage*, with renal function less than 20 per cent normal there is only one outcome: this is uremia, unless exitus is hastened by cardiac failure or other intercurrent cause. The time in which the end is reached, however, varies greatly. Thus cases 22 and 23 plunged directly from acute nephritis into the terminal stage and reached uremia in 5 and 3 months after the acute onset. On the other hand case 29 lived for two years in the terminal stage and when last seen was still capable of carrying on his work as a waiter, although during the two year period his clearance gradually shrank from 20 per cent of normal to 10. He exemplifies the fact that *one can maintain bodily*


No. 13 D.G., Hospital No. 5186, ♂, 29 yrs.
Hemorrhagic Acute → Latent
Acute
Latent
Tonsillectomy
No. 14 A.S. Hospital No 5295, ♂, 29 yrs
Hemorrhagic Acute → Latent
No. 15 F.C. Hosp. No. 5441, ♂, 25 yrs
Hemorrhagic. Acute
Lat. or Act. chr.
No. 16 J.Y. Hospital No 5538, ♀, 25 yrs
Hemorrhagic Acute → Latent
No. 17 R.G. Hospital No. 5482, ♂, 11-12 yrs
Hemorrhagic Acute → Active chronic
Active chronic
Mastoidectomy
Adenoidectomy
Hemoglobin
Vol. per cent O2
Urea Cs
Cc. blood per min.
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months

CHARTS 13–17

activity with 10 per cent of normal urea excreting power, so long as other complications, in particular the degenerative syndrome, are not present in addition to the glomerular loss.

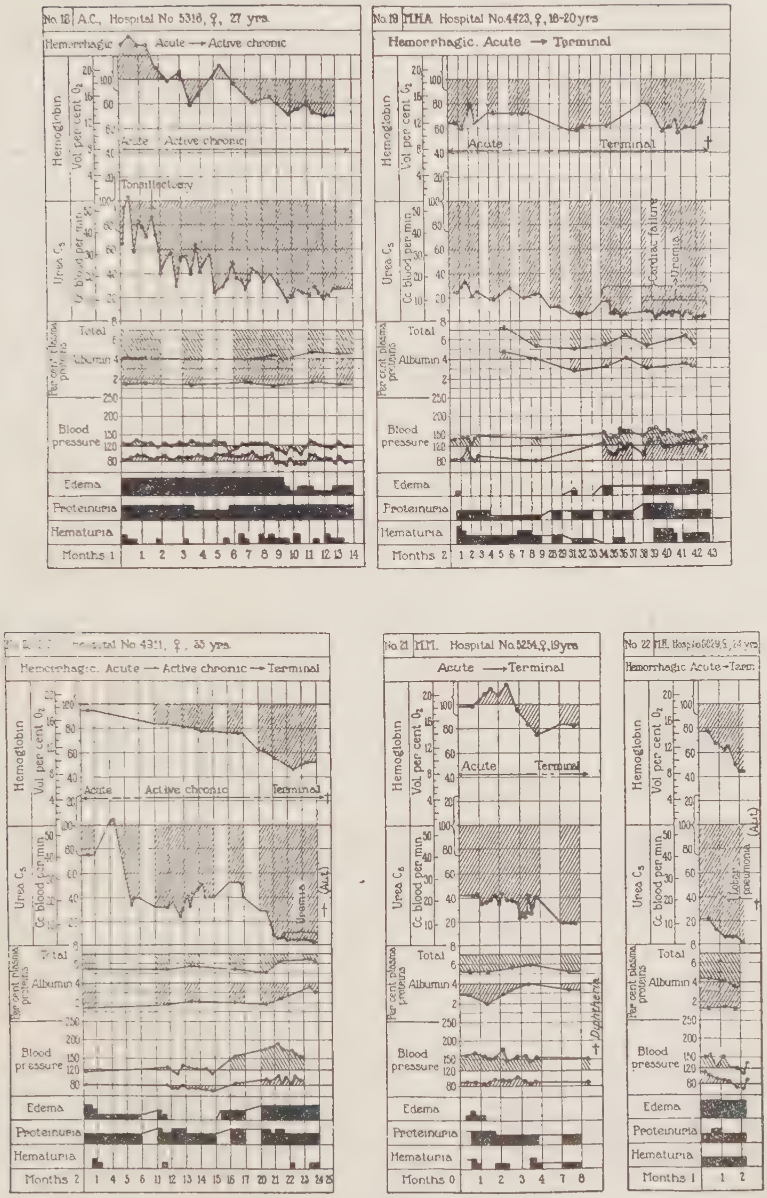
When, however, the blood urea clearance falls to 5 per cent of normal uremia appears to be inevitable.

Hematuria in hemorrhagic nephritis

Every case admitted during the first weeks of the *acute* stage showed hematuria, in most cases macroscopic. (Case 16 admitted 7 months after onset with only an occasional trace of microscopic hematuria had also a history of bloody urine at onset.) *The degree of initial hematuria appeared to have no relation to the prognosis.* Of the first four cases, which showed apparently complete recovery under observation, 3 had gross macroscopic hematuria. Nor does the period of persistence of hematuria appear to have any close relationship to the outcome. In the first three cases, those who most quickly recovered, it is true that hematuria disappeared in two to four months. A similar disappearance, however, occurred in cases 18 and 20, which went down into the active chronic and eventually the terminal stage. These latter cases showed recurrences of slight microscopic hematuria, and probably by the Addis sediment count would have shown a persistent quantitatively abnormal output of red cells. Nevertheless the hematuria assuredly subsided quickly to a slight one while the disease continued its progress at a fairly rapid rate towards a fatal conclusion.

Of the cases observed to improve to the *latent condition* (nos. 6 to 16) hematuria was observed to disappear during the periods of observation (4 to 34 months from acute onset) only in 5 of the 11. In all of the others it fell to microscopic proportions except in no. 11, who was observed for only four months, and in this case hematuria was decreasing.

Because of the fact that during improvement to the latent condition hematuria and hypertension frequently disappear before albuminuria, plasma protein deficit, and the tendency to edema show much improvement, one can easily make the error of diagnosing such a case as nephrosis, unless the history of initial hematuria is known. Cases 13 and 16 were for several months distinguishable from pure nephrosis only by the fact that they had histories of initial hematuria.


No. 18 A.C., Hospital No 5318, ♀, 27 yrs.
Hemorrhagic Acute → Active chronic
Acute Active chronic
Tonsillectomy
No. 19 M.H.A. Hospital No. 4423, ♀, 18–20 yrs
Hemorrhagic. Acute → Terminal
Acute Terminal
Cardiac failure
Uremia
Hospital No 4311, ♀, 33 yrs.
Hemorrhagic. Acute → Active chronic → Terminal
Acute Active chronic Terminal
Uremia (Aut.)
No. 21 M.M. Hospital No. 5254, ♀, 19 yrs
Acute → Terminal
Acute Terminal
Diphtheria
No 22 M.R. Hospital
Hemorrhagic Acute → Term.
Lobar pneumonia (Aut.)
Hemoglobin
Vol per cent O2
Urea Cs
Cc blood per min
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months

CHARTS 18–22

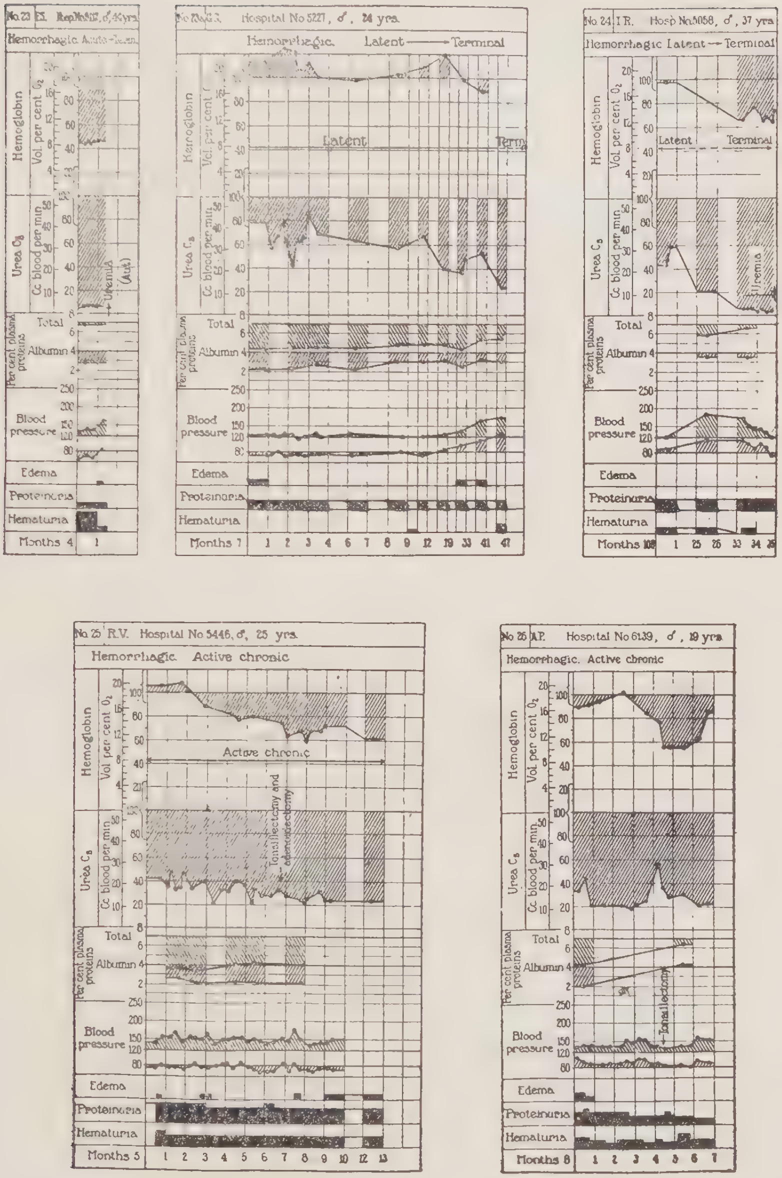
In the *active chronic stage of hemorrhagic nephritis again the degree of hematuria appears to bear no relation to the severity or rate of progress of the disease.* Case 17 showed the heaviest hematuria of any in this stage, but the progress of his disease, as shown by his clinical condition and blood urea clearance, was not unusually rapid. Case 20 after the twentieth month of observation began to suffer a rapid decrease in clearance leading five months later to death in uremia. Yet during this period of rapid downward progress there was no hematuria detectible by ordinary microscopic examination. Case 20 was in fact for some time after admission considered to be probably a nephrosis. The occasional occurrence of microscopic hematuria, the development of a marked fall in urea clearance, and then of an increase in blood pressure, however, eventually led us to conclude that it was probably a case of hemorrhagic nephritis in which for the time the degenerative element dominated the picture, a conclusion which was confirmed by autopsy.

In the *terminal stage microscopic hematuria was present in all cases,* and determinable by ordinary examination. It was sometimes marked but usually slight, and bore no relation to the rate of progress of the clinical symptoms or the functional fall indicated by the blood urea clearance.

In our cases therefore hematuria was constant and usually gross in the acute stage, and constant but microscopic in the terminal. During the intermediate chronic active stage, and during improvement from the acute stage, hematuria may disappear, or at least become so slight that ordinary microscopic examination, without Addis' (1925) special precautions, fails to reveal it. *Cases in which hematuria thus disappears may be for a time indistinguishable from non-hemorrhagic degenerative Bright's disease (nephrosis) in every respect except their histories of acute hemorrhagic onset.*

Blood pressure in hemorrhagic nephritis

Acute and latent stages. Of the 16 acute cases which recovered or improved to the latent condition (nos. 1 to 16) all except three, nos. 6, 10 and 11 showed at onset some hypertension (no. 5 showed only 130 mm. systolic but this is excessive for a three year old child). It is quite possible that nos. 6, and 10 may have had initial hypertension


No. 23 E.L. Hosp. No. 5122, ♂, 4 yrs.
Hemorrhagic Acute-Term.
Hospital No 5227, ♂, 24 yrs.
Hemorrhagic. Latent → Terminal
Latent
Term
No. 24 I.R. Hosp No. 5058, ♂, 37 yrs.
Hemorrhagic Latent → Terminal
Latent
Terminal
Uremia
Uremia (Aut.)
No. 25 R.V. Hospital No 5446, ♂, 25 yrs.
Hemorrhagic. Active chronic
Active chronic
Tonsillectomy and adenoidectomy
No. 26 A.P. Hospital No 6139, ♂, 19 yrs.
Hemorrhagic. Active chronic
Tonsillectomy
Hemoglobin
Vol. per cent O2
Urea Cs
Cc. blood per min.
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months

CHARTS 23–26

which disappeared by the time of admission, since the latter occurred six and four weeks after onset, respectively. No. 11, however, was admitted a week after onset with normal pressure. Of the 15 acute cases with favorable outcome on which we have early data, 13 therefore showed some elevation of blood pressure. Usually systolic and diastolic were elevated by similar heights. The systolic level reached was generally between 150 and 170 mm., but in no. 9 it approached 200.

The *duration of the hypertension* in these favorable cases was usually four to six weeks from the acute onset. In two cases, nos. 1 and 12, however, the pressure did not return permanently to normal, normal blood urea clearance being nevertheless thus far maintained. (Note: Patient No. 1 has since been examined, 2 years after the last observation noted on his chart, and his blood pressure has been found entirely normal, 118 systolic and 80 diastolic.)

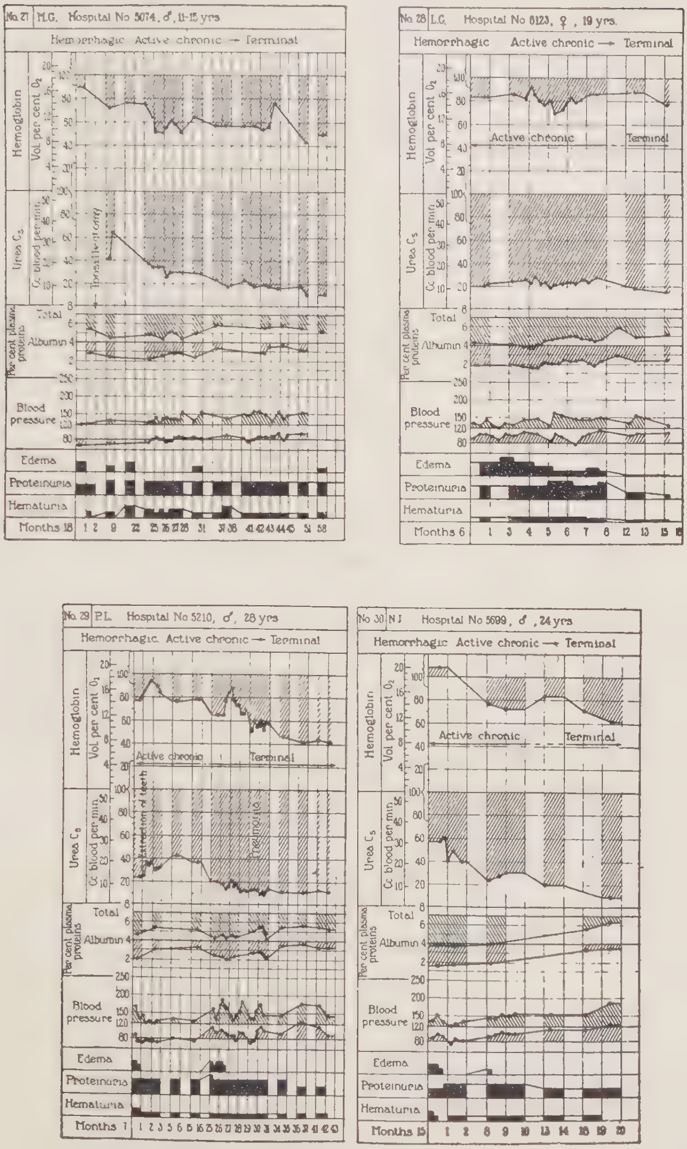
Of the four cases, nos. 17 to 21, which passed during observation from acute into active chronic, three showed during the acute stage normal blood pressures, which in no. 18 persisted through the active chronic stage for at least a year, during which the renal function showed a steadily downward progress.

One can not ascribe any prognostic value to the initial blood pressure level observed during the first weeks of acute hemorrhagic nephritis. A case which shows little or no initial hypertension appears likely to pass into the chronic state as well as the one that does show hypertension in the acute stage; likewise recovery may occur in either case.

Two cases (nos. 12 and 15) showed for periods of 2 or 3 months definite hypotension, 90 to 100 mm. systolic and 40 to 60 diastolic. No. 12, a 7 year old girl, later developed a hypertension (systolic up to 200 mm.), thus far with normal urea excreting power maintained.

In the *active chronic stage* (cases 17, 18, 20 and 25 to 31), of ten cases, three showed no hypertension, while the other seven showed slight blood pressure increases, mostly in the neighborhood of 150 mm. systolic.

Of the 21 cases (19 to 50 inclusive, except 25) observed in the *terminal state of hemorrhagic nephritis* 13 showed blood pressures definitely above 150 mm. systolic, while eight did not (nos. 22, 23, 27, 28, 33, 35, 43 and 46). Most of these did show slight hypertensions, in the


No. 27 M.G. Hospital No 5074, ♂, 11-15 yrs
Hemorrhagic Active chronic → Terminal
Hemoglobin
Vol per cent O₂
Urea Cₛ
cc blood per min
Tonsillectomy
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months 18 1 2 9 22 25 26 27 28 31 37 38 41 42 43 44 45 51 58
No. 28 L.C. Hospital No 6123, ♀, 19 yrs.
Hemorrhagic Active chronic → Terminal
Active chronic
Terminal
Months 6 1 3 4 5 6 7 8 12 13 15 16
No. 29 P.L. Hospital No 5210, ♂, 28 yrs
Hemorrhagic Active chronic → Terminal
Active chronic
Terminal
Extraction of teeth
Pneumonia
Months 7
No. 30 N.I. Hospital No 5699, ♂, 24 yrs
Hemorrhagic Active chronic → Terminal
Active chronic
Terminal
Months 15 1 2 8 9 10 13 14 18 19 20

Charts 27–30

neighborhood of 150 systolic, but cases 33, 43 and 46 reached uremic deaths without blood pressures that could be called definitely abnormal at all.

Of the cases (nos. 38, 41 and 47) that showed systolic blood pressures over 200 mm. and came to autopsy, all showed marked arteriolar sclerosis in the kidneys.

Branch and Linder (1926) reported autopsies on 7 cases dying in uremia, with blood pressures regularly over 160/110 except during final collapse. In six of the seven arteriolar sclerosis was present.

According to the results of Branch and Linder (1926) and our own, permanent marked hypertension developing during chronic hemorrhagic nephritis usually indicates the addition of an arteriosclerotic element to the pathology of the disease. So far as can be judged by comparison of clearance changes in hemorrhagic cases with and without marked hypertension, however, the rate of renal destruction does not seem to progress significantly faster in the former than in the latter. Hypertension does indeed add its symptoms to the clinical picture, but uremia does not appear to come on much, if any, more rapidly than in cases without hypertension. Thus case 46, without hypertension or any other sign of circulatory disturbance, reached a fatal uremia in a year after his clearance was found between 10 and 20 per cent of normal; while case 38, with marked hypertension and renal arteriosclerosis (found at autopsy), lived for two years after her clearance was found at the same level.

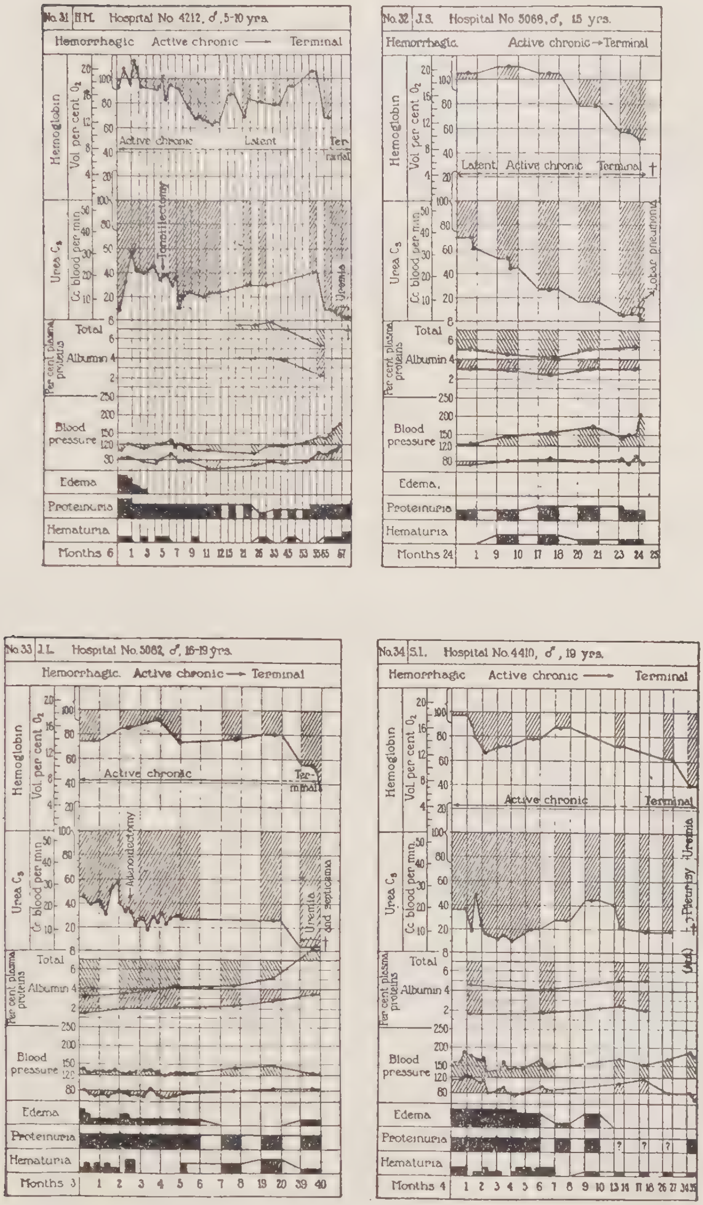
From the above data the following conclusions appear derivable.

Hypertension occurs in most, but not all, cases with active hemorrhagic (glomerular) nephritis, acute or chronic.

In the inactive, latent cases hypertension is usually, but not always, absent.

In the terminal stage a marked rise of blood pressure occurs in many cases (e.g., nos. 24, 30, 31, 32, 36, 37, 40, 48 and 49) a few months before uremic death. Terminal cases which do not show such a change in blood pressure likewise have a bad immediate prognosis, however.

A marked *fall* in blood pressure is not uncommon in the last weeks or days of terminal nephritis in cases that have previously had hypertension (cases 24, 35, 39, 42 and 50). Such a fall is presumably a sign of heart failure.


No. 31 H.M. Hospital No. 4212, ♂, 5-10 yrs.
Hemorrhagic Active chronic → Terminal
Active chronic
Latent
Terminal
Tonsillectomy
Uremia
No. 32 J.S. Hospital No. 5068, ♂, 15 yrs.
Hemorrhagic Active chronic → Terminal
Latent
Active chronic
Terminal
Lobar pneumonia
No. 33 J.L. Hospital No. 5082, ♂, 16-19 yrs.
Hemorrhagic. Active chronic → Terminal
Active chronic
Terminal
Adenoidectomy
Uremia and septicemia
No. 34 S.I. Hospital No. 4410, ♂, 19 yrs.
Hemorrhagic Active chronic → Terminal
Active chronic
Terminal
Pleurisy
Uremia
Hemoglobin
Vol. per cent O₂
Urea C₃
Cc. blood per min.
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months

Charts 31–34

Hemorrhagic nephritis can in exceptional cases run its entire course from acute onset to final uremia without definite hypertension. Our data on this point confirm those of Bannick (1927).

At no stage in nephritis primarily of the hemorrhagic type does blood pressure have definite prognostic significance concerning the fate of renal function or the rapidity of approach of uremia.

The definite significance that does attach to hypertension is that it marks the type of case in which death may occur from circulatory failure before renal failure has reached a lethal degree, or in which death may occur from a combination of cardiac and renal failure, as in cases 41 and 47.

Plasma protein content in hemorrhagic nephritis

In some *acute* cases the plasma proteins are practically unaffected. Such a condition appears to augur a good prognosis. Of our 23 acute cases the four which showed no fall in plasma proteins, nos. 1, 5, 8 and 11, all either recovered or improved to the latent stage.

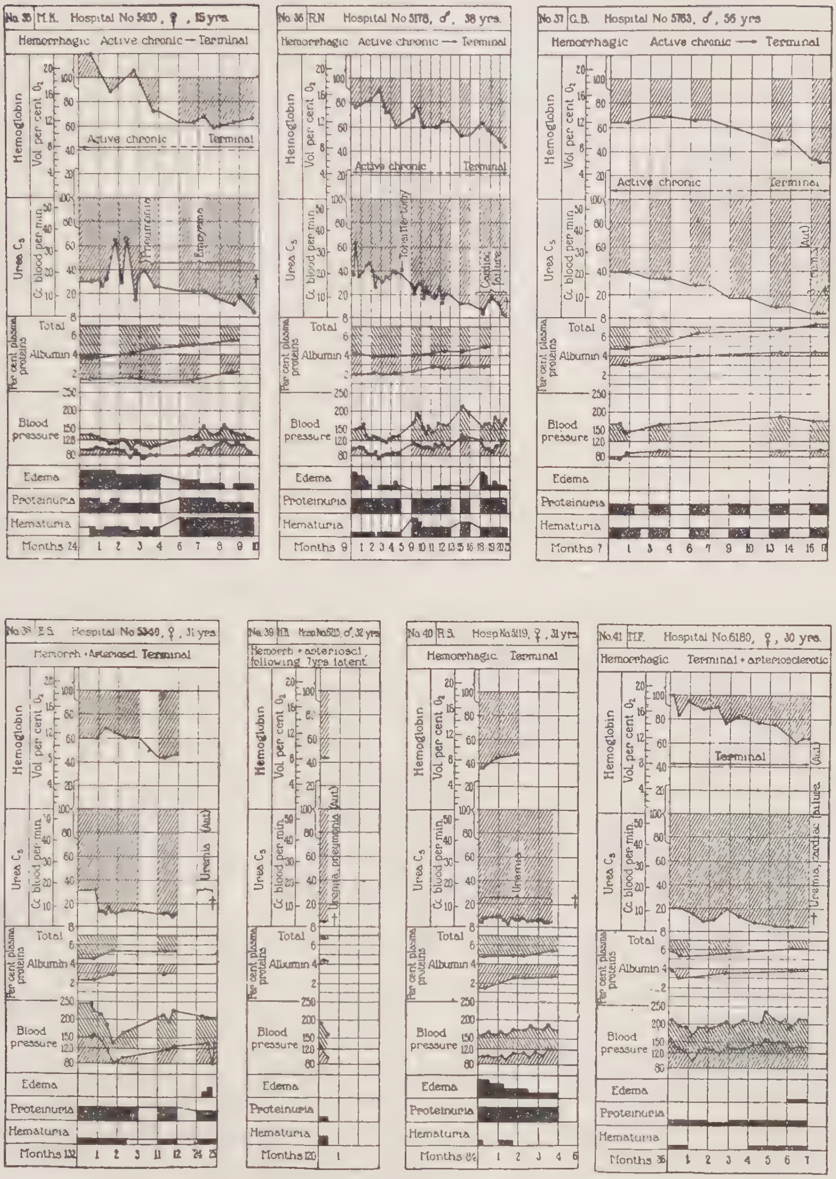
Of the 23 acute cases, 16 maintained plasma albumin contents above 2.2 per cent. Fourteen of these 16 (nos. 1 to 14) either recovered or improved to the latent condition. Only nos. 19 and 21 failed to do so.

In seven cases the plasma albumin fell definitely below 2.2 per cent. Of these cases, 5, all except nos. 15 and 16, progressed into the active chronic stage, and nos. 15 and 16 appeared the least promising of those that improved to the latent stage.

If we draw the line for *total proteins* at 5.5 per cent the division is nearly the same, but not quite so sharp.

Unlike the urea excreting power and degree of hematuria, therefore, plasma protein content appears to be of decided prognostic significance during the acute stage of hemorrhagic nephritis. *Acute hemorrhagic cases that maintain plasma albumin above 2.2 per cent, or total protein above 5.5, have a better prognosis than those that do not.* Of our cases in the group with over 2.2 per cent albumin only 13 per cent developed into progressing chronic or terminal nephritis, while of our cases in the group with less albumin 72 per cent so developed.

Cases 6 to 16 were observed *during improvement from the acute to the latent stage.* It appears that during the latent condition there is no


No. 35 M.K. Hospital No 5400, ♀, 15 yrs.
Hemorrhagic Active chronic → Terminal
No. 36 R.N. Hospital No 5178, ♂, 38 yrs.
Hemorrhagic Active chronic → Terminal
No. 37 G.B. Hospital No 5763, ♂, 56 yrs.
Hemorrhagic Active chronic → Terminal
No. 38 E.S. Hospital No 5349, ♀, 31 yrs
Hemorrh. + Arteriosel. Terminal
No. 39 H.R. Hosp No 5215, ♂, 32 yrs
Hemorrh. + arterioscl. following 7 yrs latent
No. 40 R.S. Hosp No 5119, ♀, 31 yrs
Hemorrhagic Terminal
No. 41 T.F. Hospital No. 6180, ♀, 30 yrs.
Hemorrhagic Terminal + arteriosclerotic
Hemoglobin
Vol per cent O_2
Urea C_s
Cc. blood per min.
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months
Active chronic
Terminal
Pneumonia
Empyema
Tonsillectomy
Cardiac failure
Uremia
Uremia, pneumonia
Uremia, cardiac failure
(Aut)
†

CHARTS 35–41

tendency for plasma albumin deficit to develop, and that if plasma protein deficit has been retained from the acute stage slow rise of protien content to normal occurs. Such a rise is observed in cases 10, 13 and 16. From the time of acute onset until the plasma protein contents could be considered within the normal range, required 9, 17 and 20 months respectively in these three patients.

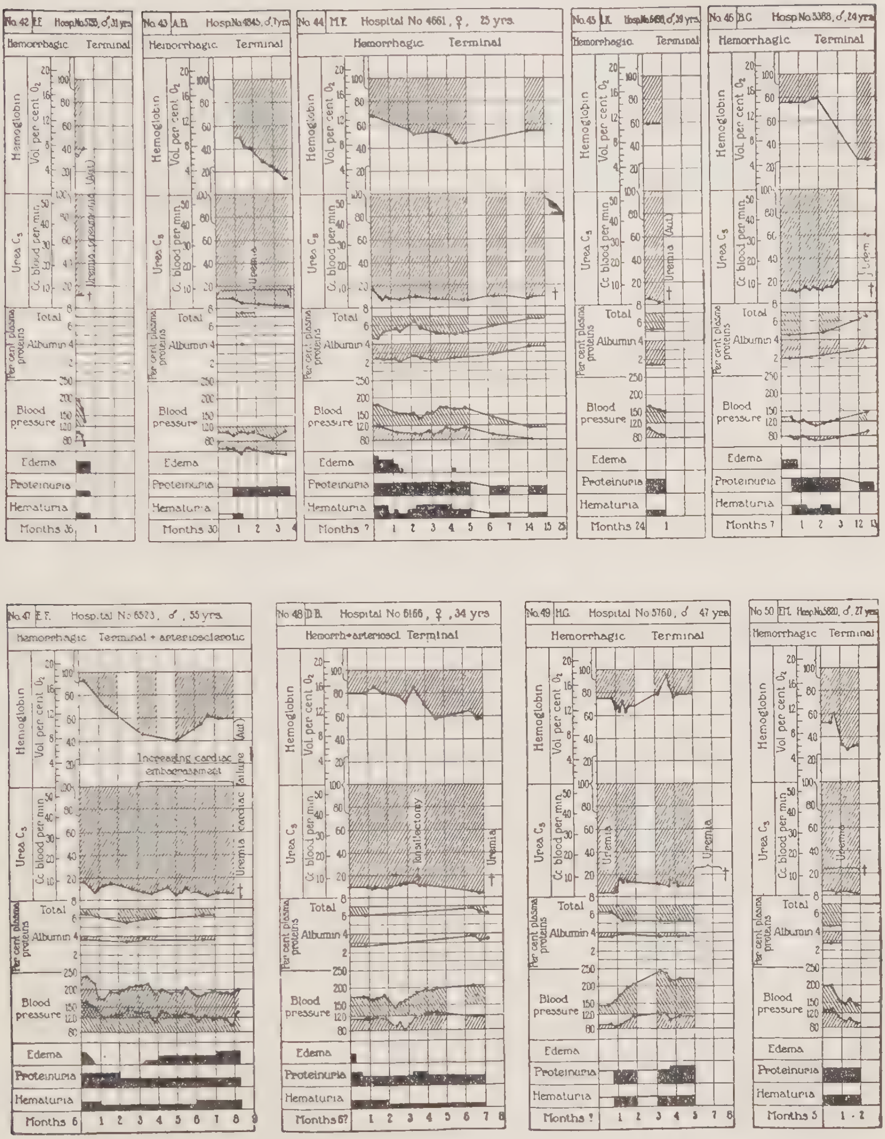
It appears probable that most cases in the *active chronic* stage develop from those which already have plasma albumin deficit during the preceding acute stage, and that the deficit developed in the acute stage is maintained in the active chronic. Examples are seen in cases 17, 18 and 20, which we were able to observe during passage from acute to active chronic.

All of the 16 active chronic cases in which plasma proteins were determined (nos. 17, 18, 20, 25 to 30 and 32 to 37) show plasma albumin deficits. In two cases (nos. 32 and 37) the albumin content fell only to about 3 per cent, but in the other 14 it was below the 2.5 per cent which appears to be the critical level for the appearance of the tendency to edema formation. The deficit in total protein, as in the acute stage, roughly parallels in most cases that in albumin, indicating that the globulin content is relatively unaffected. In case 25, however, the globulin content is also unusually low, causing a greater deficit in total protein than in albumin, while in case 20 the reverse occurs, the globulin being increased to nearly 4 per cent.

In case 31, which was admitted during the chronic active stage, there were unfortunately no plasma protein determinations done until two years later, when the case had become latent. This case was admitted during the earlier years of the work, before plasma protein determinations were routinely performed. From the massive edema and heavy proteinuria observed at admission, it appears probable that the usual plasma albumin deficit existed.

It appears evident that *a low plasma albumin content, usually below the 2.5 per cent level at which albumin deficit begins to produce edema, is the rule in the active chronic stage of hemorrhagic nephritis.*

As the active chronic stage passes into the terminal hemorrhagic there is a marked tendency for the plasma proteins to rise towards normal (cases 26, 27, 28, 29, 30, 32, 33, 35, 36 and 37). *In about half the terminal cases in our series* (see nos. 19 to 49) *the plasma proteins, both total and albumin, reached normal limits before death occurred.*


No. 42 E.F. Hosp. No. 5755, ♂, 31 yrs.
Hemorrhagic Terminal
No. 43 A.B. Hosp. No. 4845, ♂, 7 yrs.
Hemorrhagic Terminal
No. 44 M.F. Hospital No 4661, ♀, 25 yrs.
Hemorrhagic Terminal
No. 45 L.K. Hosp. No. 5466, ♂, 39 yrs.
Hemorrhagic Terminal
No. 46 B.C. Hosp. No. 5388, ♂, 24 yrs.
Hemorrhagic Terminal
No. 47 E.F. Hospital No 6523, ♂, 55 yrs.
Hemorrhagic Terminal + arteriosclerotic
No. 48 D.B. Hospital No 5166, ♀, 34 yrs
Hemorrh. + arterioscl. Terminal
No. 49 H.G. Hospital No 5760, ♂ 47 yrs
Hemorrhagic Terminal
No. 50 E.M. Hosp. No. 5820, ♂, 27 yrs
Hemorrhagic Terminal
Hemoglobin
Vol per cent O₂
Urea C₅
Cc. blood per min.
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months
Uremia
(Aut.)
Tonsillectomy
Increasing cardiac embarrassment
Cardiac failure
†

CHARTS 42–50

Proteinuria in hemorrhagic nephritis

In *acute hemorrhagic nephritis the degree of initial proteinuria appears to have no prognostic significance.* Of the 23 acute cases, the 3 which showed minimal proteinuria (nos. 1, 7 and 8) all improved; but likewise did the 3 (nos. 11, 13 and 15) who showed maximal proteinuria of more than 10 grams per 24 hours. Of the cases with intermediate degrees of protein output some recovered and some progressed.

The *duration* of the proteinuria in the cases which completely recovered (nos. 1 to 5) was from 2 weeks to 5 months.

In all the acute cases which improved to the *latent stage* (nos. 6 to 16) proteinuria persisted, but showed a marked diminution from the initial output.

In the 3 cases that passed while under observation from the acute into the *active chronic* stage (nos. 17, 18 and 20) there was no marked change in the proteinuria. In general the protein excretion in the active chronic stage is from 2 to 15 grams per day. Occasionally a single case will fluctuate over nearly this entire range within a month (data not shown on charts), but the protein content of the urine never decreases to the trace that is seen in arteriosclerotic and a few terminal hemorrhagic cases.

Terminal stage. In the 3 cases that we have seen pass directly from the acute into the terminal stage (nos. 19, 21 and 22) there has been no significant change in the protein output.

Likewise in the majority of cases passing from the chronic active into the terminal stage the protein excretion continues about the same (nos. 17, 20, 24, 25, 27, 31, 32, 33, 35, 36 and 37). However, in a considerable minority there is a decrease in protein output (nos. 26, 28, 29, 30, 39 and 44). In about one case out of five (nos. 23, 39, 41 and 42) the urinary protein sinks to a trace during the final period.

Edema in hemorrhagic nephritis

Acute stage. In the introductory discussion of the significance of plasma protein concentration and edema the relationship of the two has already been presented, together with the fact that an exception to this relationship occurs in the *initial period* of acute hemorrhagic nephritis, where *temporary edema occurs even in cases that do not show* *sufficient deficit of albumin in the plasma to produce of itself edema.* Cases 1 to 9 all show this type of edema, with plasma albumin above 2.5 grams per 100 cc. of plasma. In cases 5 and 8 the plasma proteins were at full normal concentration. It is evident that the initial edema of acute nephritis is attributable in part, and in some cases entirely, to some factor of this frequently toxic period other than lack of plasma albumin.

Such initial edema unaccompanied by plasma albumin deficit appears to be temporary. In all the above cases it disappeared within two months of the onset of the disease, and in case 5 within two weeks.

In cases 10, 12, 13, 14 and 16, edema disappeared at the same time that the plasma albumin showed definite increase. The increase is frequently not very marked on the charts, partly because of the small scale of the latter, partly because a relatively slight increase in the neighborhood of the critical level (albumin about 2.5 per cent) has a great effect in diminishing the tendency to store fluid.

Cases 18 and 22 exemplify persistent edema combined with continued plasma protein deficit. Salt restriction and other therapy were unsuccessful in overcoming the retention.

In cases 17 and 20 edema disappeared under treatment despite continued plasma protein deficit. It recurred at times, however, for no apparent reason, despite continual salt restriction. The tendency to edema was obviously present and fairly intense.

Latent stage. In all our latent cases (nos. 6 to 16 inclusive and 24) edema was absent, and plasma proteins were above the critical levels.

Chronic active stage. In this condition the tendency to edema is ordinarily one of the most outstanding characteristics, although a small minority of cases do not show it. Out of 17 chronic active patients in our charts 14 showed plasma albumin below 2.5 per cent. These were all either edematous, or potentially edematous and free from fluid retention only under the influence of salt restriction, sometimes reenforced by other treatment, such as daily urea administration. The correspondence between edematous *tendency* and plasma albumin deficit in this class of cases is practically uniform.

In treated cases with plasma proteins below the critical levels edema may or may not disappear. It appears to depend partly upon how low the plasma albumin sinks, partly upon other factors.

Case 25 presents an interesting example of a patient under continuous and practically uniform treatment, with plasma albumin somewhat below the critical level, who was obviously on the verge of edema, which came and went repeatedly in the course of several months. When admitted he had edema of the face, and pitting edema of the legs and sacrum; no ascites. This edema disappeared quickly under treatment. Three months after admission 3 grams of salt were added to the hitherto salt-free diet, and edema of the same sort recurred. The salt was removed, and the edema disappeared. Three months later a tonsillectomy was performed. During the month following the operation edema gradually developed, and then quickly went away. Two months later it was present again, this time without any obvious reason.

In *terminal hemorrhagic nephritis*, as shown above, plasma albumin deficit is much less common than in the active chronic stage of the disease, and edema is correspondingly less frequent. Of our thirty cases observed during the terminal stage (nos. 19 to 24 and 27 to 50) only 10 showed marked edema. Of these but 3 (nos. 22, 35 and 46) were attributable to plasma protein deficit. Four were associated with cardiac failure (nos, 19, 36, 38 and 41), and it was probably an element in 20 and 42. The remaining case, No. 33, was complicated by streptococcus septicemia at death: his plasma proteins were at this time normal. It appears that *in the terminal stage edema, when it occurs, may be due either to cardiac failure or to plasma protein deficit. In our series the number apparently due to cardiac failure was greater.*

Anemia in hemorrhagic nephritis

In the *acute* stage there is a considerable degree of correlation between the anemia and the degree of fall in renal function indicated by the blood urea clearance. The most marked anemias were shown by cases 4, 10, 11, 12, 14 and 19, in which the hemoglobin fell to 45 to 75 per cent of Haldane's normal average and the urea clearance fell to 5 to 25 per cent of average normal. However, blood urea clearance in case 9 fell to 4 per cent of normal and uremic symptoms became severe, without fall of hemoglobin below 80 per cent, and in case 8 the clearance fell to 30 to 40 per cent with maintenance of a perfectly normal hemoglobin content. A good hemoglobin value in acute nephritis does not therefore by any means indicate a well maintained renal function. *In prognosis the temporary anemia of the acute stage is of no more significance than the temporary fall in blood urea clearance,* which has already been discussed. And the absence of anemia is likewise no guarantee of a mild course or favorable outcome.

In the acute cases which showed anemia but later improved or recovered, the minimum hemoglobin content occurred two to four months after the acute onset.

In the *latent stage* (cases 6 to 16 and 24) anemia is absent or slight.

In the *active chronic* stage (see cases 16 to 37), as in the acute, anemia is accompanied by a decreased blood urea clearance, the value of the clearance, expressed in per cent of normal, being usually a half to a third of the hemoglobin expressed in the same way. Again, as in the acute stage, the reverse does not hold; there may be low blood urea clearance with little or no anemia. In almost every active chronic case periods are seen when the clearance was below 40 per cent normal while the hemoglobin was above 80 per cent.

With prolonged duration of low renal function the hemoglobin often shows a later and much slower fall than the clearance. Case 32 illustrates such an occurrence. The disease had apparently been latent or slowly progressing, and at the first examination the clearance was 70 per cent of normal, almost within the normal minimum, and hemoglobin was 105 per cent. During 18 months the clearance fell steadily to 28 per cent of normal, while the hemoglobin remained at 105 to 110 per cent. However, during the terminal six months following, when the clearance fell to almost zero and uremia developed, the hemoglobin fell progressively to 50 per cent.

In the *terminal stage* of hemorrhagic nephritis anemia is practically always present. When uremia is reached the oxygen capacity in our terminal cases had usually fallen to between 6 and 12 volumes per cent (32 to 64 per cent of Haldane's normal average). In case 43 the oxygen capacity fell rapidly during the final weeks and was down to 3 volumes per cent at death. On the other hand, case 49, after being for six months either on the verge of uremia or in it, died with but a relatively slight anemia of 14.5 volumes per cent oxygen capacity, 78 per cent of Haldane's normal average.

In summary, one can say that in chronic nephritis the oxygen capacity of the blood seldom falls below 15 volumes per cent without the concurrence of a marked deficit in urea excreting ability, and of a condition bearing a grave prognosis. However, the relationship between the degree of anemia and the loss of renal function or the probable duration of life is most irregular, occasional cases making, as shown by the progressive fall of blood urea clearance and the clinical signs, an obviously inevitable approach to uremic death with but slight fall in blood hemoglobin content. *While the presence of anemia signifies a grave prognosis, the maintenance of nearly normal hemoglobin does not gainsay the immediate onset of uremia.*

ANATOMICAL CHANGES OBSERVED IN TERMINAL HEMORRHAGIC NEPHRITIS[3]

Of the 50 cases of hemorrhagic nephritis which we report 25 died and autopsies were permitted on 11 (nos. 20, 22, 23, 34, 37, 38, 39, 41, 42, 45 and 47). Two passed into the terminal stage directly from the acute, while the other 9 first passed through more or less prolonged periods in the intermediate active chronic stage before they reached the terminal.

In every case practically all of the glomeruli were destroyed. This finding, taken with the fact that the blood urea clearance was reduced to the neighborhood of 5 per cent of normal or lower in these terminal cases, indicates the probability that *in hemorrhagic nephritis the fall in blood urea clearance is proportional to the glomerular destruction.*

Five of these cases, nos. 38, 39, 41, 45 and 47, were clinically classified, because of *marked hypertension and cardiac enlargement*, as arteriosclerotic in addition to the primary hemorrhagic disease. *All of these cases showed, in addition to the glomerular destruction, marked arteriolar changes at autopsy.*

The two cases, nos. 22 and 23, which went from the acute stage directly into the terminal, in contrast to the other nine, did not show contracted kidneys, although glomerular destruction was practically complete. The kidneys were of the large white type, and corresponded histologically with the descriptions by which Volhard and Fahr (1913) and

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[3] Detailed reports of the autopsy examinations are given below with the case histories.

Ophüls (1916) distinguished what they term the subacute or subchronic form of glomerulonephritis.[4]

Diffuse hemorrhagic glomerulonephritis is generally classified by pathologists into three stages. Volhard and Fahr (1914) and Ophüls (1916) distinguish an acute, a subchronic (or subacute) and a chronic glomerulonephritis, whereas Aschoff (1921) discriminates an acute inflammation, a stage of regeneration and reparation, and a stage of scar formation. The second stage of all writers corresponds to the large white or mottled kidneys, whereas the third stage corresponds to the secondary contracted kidneys.

It is sometimes difficult in individual cases to decide by autopsy which stage is present. This is true especially in subchronic and chronic stages. Fahr presents in his handbook (1925) such a case which anatomically resembled the second (subchronic) stage. But because of a duration of three to four years he ascribed this case to the chronic stage. Generally one might speak of a third stage (terminal chronic) when, macroscopically, the consistency of the kidneys becomes firmer and the differentiation between cortex and medulla more indistinct; when, histologically, the parenchyma becomes wasted to a large extent and the glomeruli irregular in size and lesion. In the chronic stage the kidneys may still be enlarged (as in case 20). But usually one finds all transitions of extensive shrinkage.

Except cases 41 and 47, all cases of this group were pure glomerulonephritis. *The outstanding lesions were diffuse changes of all or nearly all glomeruli.* Vascular lesions of degenerative nature were absent or insignificant.

Cases 22 and 23 showed anatomical changes characteristic for the subchronic stage. These were, as mentioned above, cases of short duration. They passed clinically directly from the acute to the terminal stage, and died with nitrogen retention three and five months respectively after acute onset. The kidneys were large and white with occasional blood dots on their surfaces. The consistency was doughy.

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[4] Our findings agree entirely with the statements of Volhard and Fahr (1914) concerning the lack of relationship between degree of functional deficit of the kidneys and the amount of gross anatomical contraction, also with their statement that the degree of contraction depends more on the duration of the disease than on the degree of functional damage that the kidneys have suffered.

The cortex was well marked off from the medulla. Histologically it was found that the renal architecture was still well preserved. There was only a slight scar formation. Case 22 belonged to the intracapillary, and case 23 to the extracapillary form. The glomeruli of case 22 were unusually rich in fibrinoid substances. Many of the tubules were degenerated in both cases. The vascular changes were insignificant. Case 23 showed only a slight cardiac hypertrophy and case 22 none at all. Both cases died with bronchopneumonia, but uremic symptoms were already present in one and, from the low level of the blood urea clearance, appeared inevitable in the other.

In the remaining cases death occurred only after the disease had run the usual more prolonged course, through the chronic active stage to the terminal. The histological changes likewise belonged to the chronic stage. Only in case 20, of two years duration, was it doubtful whether one should ascribe it, from the histology, to the second or to the third stage. The kidneys still were much enlarged and pale in color. But the consistency was already firmer, the surface was very finely granulated, and the differentiation between cortex and medulla was no longer distinct. Also, a marked cardiac hypertrophy was already present. The deciding factor for our diagnosis of a third stage (terminal at end of chronic glomerlar) was the histology showing an extended destruction of the renal architecture (fig. 1). The outstanding lesion of the glomeruli was a diffuse hyalinization of the loops.

Case 42 is a further example of beginning shrinkage. On the one hand, the kidneys were already decreased in weight and their surfaces were slightly granulated. But, on the other hand, the kidneys were still of doughy consistency and their cortex was well marked off from the medulla. That the disease here was in the chronic stage was shown by the histology, which greatly resembled that of case 20. Also, a marked cardiac hypertrophy was found.

Cases 20 and 42 died in uremia.

The remaining 5 pure cases (nos. 34, 37, 38, 39 and 45) showed advanced contracted kidneys, which, in most instances, were grayish in color and showed both fine and coarse granulations. All were firm in consistency. The differentiation between cortex and medulla was indistinct or missing. The cases all showed marked cardiac hypertrophy and all died in uremia, except one who died with confluent bronchopneumonia. Histologically, these older cases differed from those which passed directly from acute to terminal stage by the extensive destruction of the renal architecture and the greater irregularity of the glomerular changes which had occurred during the longer disease. Besides numerous entirely hyalinized glomeruli there were glomeruli which still contained one or more loops filled with blood.

As might be expected from the variety of the lesions, certain features were found which bestowed an individual aspect upon each case. In cases 34 and 38, the glomeruli were still very large and rich in nuclei, whereas in case 37 the hyalinization of the glomerular loops was outstanding. In cases 39 and 45 there was a striking slight proliferation and desquamation of glomerular epithelial cells which, according to Fahr (1925), gives the impression of a more rudimentary inflammation.

In the wasted parenchyma, islands of better preserved tubules were seen, as is well shown by figure 11. The dilatation of these tubules is looked upon as an attempt at compensation, whereby the organism seeks to enlarge the secreting surface. Some of the epithelial cells of these tubules showed fatty degeneration, whereas hyaline-droplet degeneration was rare or missing.

The vascular changes varied a great deal in these cases. An advanced intimal hyperplasia was seen in cases 38, 39 and 45. An endarteritis was found in all cases, but reached higher degrees only in cases 38 and 39, which during life showed exceptionally high blood pressures. In case 38 also some necroses in the walls of the arterioles were seen. Hyalinization and fatty degeneration were present in all cases. But they were only slight in most instances and were not comparable to the changes which are usual in arteriolosclerosis.

Among the eleven cases autopsied in the hemorrhagic group nos. 41 and 47 were not pure cases of glomerulonephritis. The glomeruli of both cases were diffusely changed, mainly by hyalinization of the loops. But in addition both cases showed an extensive hyalinization and fatty degeneration of the arterioles, and advanced intimal hyperplasia of the medium sized and larger arteries and an endarteritis with some necroses of the small arteries. Case 41 furthermore showed a fresh pyelonephritis.

That in hemorrhagic nephritis we have to deal with a glomerulonephritis is shown by the presence regularly of diffuse disease of the glomeruli. (It is improbable that in case 41 the fresh pyelonephritis was responsible for the diffuse hyalinization of the glomeruli. According to all we know the glomerular lesions were much older than the pyelonephritis.) However, it is more difficult to decide whether the arterio- and arteriolosclerosis in cases 41 and 47 was of secondary nature or whether it existed independently of the glomerulonephritis. We are inclined to believe that it did so exist and that we have to deal in cases 41 and 47 with combined primary and secondary contracted kidneys. Aside from the fact that the arterio-, and, especially, the arteriolosclerosis, were of a high degree, the macroscopical granulation, partly caused by islands of compensatory dilated tubules, was also partly caused by scarred retractions of the parenchyma. This point is emphasized by Aschoff (1921). Furthermore, we found an advanced atherosclerosis also in other parts of the bodies of these two cases.

ABSTRACTS OF HISTORIES AND AUTOPSY REPORTS OF CASES OF HEMORRHAGIC BRIGHT'S DISEASE

A brief abstract is given of each case history covering some significant points not shown in the charts.

For each case in which an autopsy was obtained a report is also given of the post mortem observations, with microphotographs of kidney sections. Autopsies were obtained in cases 20, 22, 23, 34, 37, 38, 39, 41, 42, 45 and 47.

Case 1. Hospital No. 5312. E. A., male, 29 years. *Hemorrhagic Bright's disease.* Acute → recovery.

Three months before admission he had tonsillitis and otitis, followed by edema. Albuminuria and a blood pressure of 140 mm. were found.

On admission the otitis had cleared up. Some tonsillitis was found. The urine sediment contained many erythrocytes and erythrocyte casts and a few granular casts. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 21 mgm. per cent, blood creatinine 1.64 mgm. per cent and the basal metabolic rate −6.6 per cent. During observation the casts disappeared. The tonsils were removed without exacerbation of the Bright's disease.

Patient was reexamined 4 years after first admission. Blood pressure was 116/80 and all urinary findings negative. Nephritis apparently completely healed.

Case 2. Hospital No. 5650. S. A., female, 52 years. *Hemorrhagic Bright's disease.* Acute → recovery.

One month before admission she had a severe cold followed by empyema in the left antrum. One week before admission hematuria was found.

On admission the urine sediment contained many erythrocytes and leucocytes, some granular and erythrocyte casts. The eyegrounds were normal. Heart somewhat enlarged. Culture of the washings from the antrum showed hemolytic streptococci. Wassermann reaction was negative. Blood urea nitrogen 22 mgm. per cent, blood creatinine 1.59 mgm. per cent.

The sinus cleared up under local treatment. She was in good condition when discharged. When seen 13 months after admission the urine sediment and blood pressure were both normal.

Case 3. Hospital No. 5918. A. M., female, 23 years. *Hemorrhagic Bright's disease.* Acute → recovery.

One month before admission peritonsillar abscesses on both sides were followed by edema. Albumin, blood, and casts were found in the urine.

On admission chronic tonsillitis was found. The urine sediment contained many erythrocytes and erythrocyte casts, some leucocytes and hyaline, epithelial, and granular casts. The eyegrounds were normal. The heart was not enlarged.

During observation the number of cells and casts in the urine decreased rapidly. Seven months after admission the casts had disappeared completely.

Three months after admission the tonsils were removed, without exacerbation of patient's nephritis. She returned to hospital for examination a year after her first admission. There was no albuminuria, but a concentrated 12-hour specimen contained 1,482,000 red cells, 946,000 white and epithelial cells, and 210,000 hyaline casts. The blood pressure was 100/68.

.*Case 4.* Hospital No. 6164. R. S., male, 31 years. *Hemorrhagic Bright's disease.* Acute → recovery.

The patient was admitted because of a severe pneumonia, caused by pneumococcus Type II (atypical). During the convalescence from pneumonia an acute nephritis developed, and in the urine sediment many erythrocytes and erythrocyte casts appeared. Some hyaline and granular casts were present also during the pneumonia. Only few leucocytes were present and no doubly refractive bodies. The eyegrounds were normal. The heart size was normal. Wassermann reaction was negative. Blood urea N, 12 mgm. per cent, and plasma cholesterol, 250 mgm. per cent. During the pneumonia the blood creatinine was found to be 1.45 mgm. per cent.

In the next 2 weeks the blood urea nitrogen increased to 97 mgm. per cent and the blood creatinine to 6.29 mgm. per cent. Two weeks later the blood creatinine was 3.75 mgm. per cent. The sediment still showed some erythrocytes and erythrocyte casts. The tonsils were removed 6 months after the onset of disease, without causing a recrudescence. One month later a concentrated 12-hour specimen of urine contained no albumin, and 5,500,000 red cells, 782,000 white blood and epithelial cells, and 54,000 hyaline casts, in a 12-hour collection. The disease was considered to be latent.

Case 5. Hospital No. 6768. T. V., male, 3 years. *Hemorrhagic Bright's disease.* Acute → recovery.

The patient had had chronic bronchitis for one and one-half years. Two weeks before coming to hospital he had developed bilateral otitis media. Two days before admission gross hematuria had occurred which was accompanied by oliguria.

On admission the patient showed slight pitting edema of the lower extremities. Gross hematuria was present. Blood casts were seen in the sediment. The protein excretion in the urine was 5 grams during the first 24 hours. The blood urea nitrogen was 19 mgm. per cent. The plasma cholesterol was 319 mgm. per cent. A phenolsulphonephthalein test revealed 72 per cent return of the dye in 2 hours. The total protein of the blood plasma was 6.9 per cent.

Two days after admission the patient suffered an attack of hypertensive crisis—resulting in a temporary right hemiplegia from which he recovered rapidly. Gross hematuria disappeared on the seventeenth day. The protein excretion in the urine dropped to a trace during the first month. Blood pressure levels both systolic and diastolic dropped to normal during the first week. During the first two weeks a loss of weight (edema) to the extent of 4 kgm. occurred.

During the subsequent 4 months that the patient was observed, the number of red cells in concentrated 12-hours urine specimens became rapidly less and on discharge but 2,000,000 were found in urine passed during the last 12 hours of a 24-hour dry diet (normal is 500,000). The number of casts and white blood cells were reduced in the same proportions. Tonsillar tabs and adenoids were removed as added precaution against continued activity of the kidney lesion. The plasma proteins remained normal. The blood urea nitrogen varied between 8.1 and 19 mgm. per cent. When discharged the presence of a quantitatively slight hematuria was the only evidence of renal disease. Examination 3 months later, 8 months after onset, showed normal blood pressure, renal function and urine sediment, or apparently a complete recovery as far as could be demonstrated.

Case 6. Hospital No. 5335, C. C., male, 13 to 16 years. *Hemorrhagic Bright's disease.* Acute → latent.

Six years before admission he had acute nephritis with much edema. The attack cleared up in two months. Since then he has felt in perfect health. The urine has not been examined. Six weeks before admission hematuria and slight edema appeared.

On admission the urine sediment contained many erythrocytes and a few hyaline and granular casts. The heart size was normal. Blood urea nitrogen 22 mgm. per cent and blood creatinine 1.29 mgm. per cent.

During observation the number of casts in the sediment decreased and disappeared at the same time as the erythrocytes. The blood pressure, blood urea nitrogen and creatinine remained normal.

Four months after discharge there were still a few red cells, and hyaline casts in the urine, along with a trace of albumin. Two years after discharge, the urine showed only a very faint trace of albumin, the sediment contained very occasional red cells. The blood pressure remained normal.

Case 7. Hospital No. 5240. B. B., male, 34 years. *Hemorrhagic Bright's disease.* Acute → latent.

The last 5 years before admission he had recurrent tonsillitis. Three weeks before admission he had a peritonsillar abscess. Two days before admission edema appeared.

On admission chronic tonsillitis was found. The urine sediment contained many erythrocytes and some hyaline and granular casts. The heart was not enlarged. Wassermann reaction was negative. Blood urea nitrogen 50 mgm. per cent, blood creatinine 1.57 mgm. per cent, and the basal metabolic rate −7.1 per cent.

The number of casts decreased gradually and they disappeared between 3 and 15 months after admission. The blood urea nitrogen rapidly fell to normal. A tonsillectomy was performed, and was followed by a heavy hematuria, which cleared up in a few days. Several re-examinations showed only traces of albumin in the urine. There was still a faint trace 15 months after his first admission, although the sediment was then negative, and the blood pressure normal.

Case 8. Hospital No. 5875. N. F., male, 29 years. *Hemorrhagic Bright's disease.* Acute → latent.

For 3 weeks before admission the patient felt weak and chilly. Three days before admission edema appeared and albumin and casts were found in the urine.

On admission the urine sediment contained many erythrocytes, a few leucocytes and hyaline, granular and erythrocyte casts. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 37 mgm. per cent and blood creatinine 1.87 mgm. per cent.

In a few days the blood pressure came down to normal. After the first 2 months of observation the urine sediment showed only few erythrocytes and single hyaline and granular casts. When he was seen 5 months after onset of disease, there were still red cells, and occasional red cell and granular casts to be found. Albuminuria amounted to only a very faint trace.

Case 9. Hospital No. 5665. A. A., male, 35 years. *Hemorrhagic Bright's disease.* Acute → latent.

For many years several of his teeth have been infected and alveolar abscesses have formed. Two weeks before admission he had lumbar pain and edema; albuminuria and hematuria appeared.

On admission the urine sediment contained many erythrocytes, some leucocytes and hyaline and granular casts. The eyegrounds showed blurring of the outlines of the discs and fresh retinal hemorrhages. The heart was somewhat enlarged to the left. The gums showed gingivitis, from which Vincent's organism was obtained. Wassermann reaction was negative. Blood urea nitrogen 68 mgm. per cent, blood creatinine 1.73 mgm. per cent.

Three weeks after admission the gingivitis grew worse. For about a week there was nausea, headache and a distinct drowsiness. The blood urea nitrogen rose to 209 mgm. per cent and the creatinine to 10.84 mgm. per cent. Under local treatment the mouth cleared up, the general condition improved and in 3 months the blood urea nitrogen and creatinine decreased to normal values. Twelve and 20 months after admission the patient was in good condition and able to work 6 hours daily. The casts had decreased gradually in number and had disappeared 20 months after admission. There was albumin in the urine, amounting to 0.18 gram per liter.

Case 10. Hospital No. 5681. J. B., male, 8 to 9 years. *Hemorrhagic Bright's disease.* Initial → latent → recovered.

He has had frequent attacks of tonsillitis since the age of 4. Four months before admission edema appeared. Three months later gross hematuria was noticed.

On admission chronic tonsillitis was found. The urine sediment contained many erythrocytes, leucocytes, and granular and erythrocyte casts. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 79 mgm. per cent and blood creatinine 1.90 mgm. per cent.

Tonsillectomy was performed 3 weeks after admission. Improvement in the Bright's disease followed almost at once (see chart). The number of erythrocytes in the sediment decreased, the erythrocyte casts disappeared and the granular casts were much reduced in number. Since 5 months after admission the blood urea nitrogen and creatinine have shown normal values. Two years after admission, improvement was still taking place. There was 0.25 gram of albumin per liter in the urine, and in the sediment a few red cells, and a very few hyaline casts. The case had entered the latent phase. Three and one-half years after admission signs of renal diseases were entirely negative.

Case 11. Hospital No. 6777. R. D. F., female, 11 years. *Hemorrhagic Bright's disease.* Acute → latent.

The patient had a history of sore throats for several years—tonsillectomy and adenoidectomy had been performed 4 years previously. One year before admission a sore throat had occurred accompanied by cervical adenitis. One week previous to admission adenitis again occurred. Five days later and two days before admission gross hematuria appeared.

On admission to hospital hematuria and generalized edema were present. The blood urea N was 114 mgm. per cent. Plasma NPN 128 mgm. per cent. A phenolsulphonephthalein test revealed but a 12 per cent return of the dye in two hours. The protein excretion in the urine was 8 grams daily.

During the first month that the patient was under observation the blood urea N fell to 21 mgm. per cent. A drop in protein excretion to 1 gram per day and a decrease in weight of 6 kgm. also occurred, after which no edema was observed. Gross hematuria continued. The phenolsulphonephthalein excretion rose to 34 per cent in two hours.

During the subsequent three months the blood urea N varied between 10 and 20 mgm. per cent. Gross hematuria disappeared during the second month although red blood cells and blood casts were present in concentrated urine specimens in large numbers. Proteinuria decreased to 0.2 gram daily during the fourth month. The 2-hour phthalein excretion rose to 67 per cent before discharge from the hospital four months after onset.

Case 12. Hospital No. 5520. V. M., female, 7 years. Height 113.7 cm. *Hemorrhagic Bright's disease.* Acute → latent with hypertension.

Two weeks before admission edema appeared and albuminuria was found.

On admission chronic tonsillitis was found. The urine sediment contained many erythrocytes and erythrocyte casts, a few leucocytes and some hyaline and granular casts. Blood urea nitrogen 145 mgm. per cent and blood creatinine 2.61 mgm. per cent.

During the first month of observation the blood urea nitrogen and blood creatinine decreased to normal values. The urine sediment did not change significantly except for a decrease in the number of erythrocytes and erythrocyte casts. Tonsillectomy was carried out, and did not appear to influence the course of the Bright's disease. When the 7 year old patient was seen 20 months after admission blood pressure had risen to 160/110 and generalized arteriosclerosis and cardiac hypertrophy were noted. There were still occasional red cells in the urine, but no note of casts; albumin was only a very faint trace. The Bright's disease was considered to be latent, and the cardio-vascular disease occupied the foreground.

Case 13. Hospital No. 5186. D. G., male (colored), 29 years. *Hemorrhagic Bright's disease.* Acute → latent.

One month before admission edema was noticed.

On admission chronic tonsillitis was found. The urine sediment contained a few erythrocytes, some leucocytes and many hyaline and granular casts. The eyegrounds were normal. The heart was somewhat enlarged. Wassermann reaction was negative. Blood urea nitrogen 38 mgm. per cent, blood creatinine 1.86 mgm. per cent and plasma cholesterol 231 mgm. per cent. Five months after admission the basal metabolic rate was −16.7 per cent. The blood pressure soon fell to normal. The number of casts gradually decreased somewhat. The blood urea nitrogen remained normal; 4 months and 7 months after admission it showed minimum values of 12 and 16 mg. per cent respectively. Patient was discharged after 10 months, subjectively well. Six months later he was still well, despite continued proteinuria, and his plasma protein content had improved.

Case 14. Hospital No. 5295. A. S., male, 29 years. *Hemorrhagic Bright's disease.* Acute → latent.

Two weeks before admission the patient had peritonsillar abscesses followed by edema.

On admission chronic tonsillitis was found. The urine sediment contained many erythrocytes and leucocytes, some hyline and granular casts and a few erythrocyte casts. The eyegrounds were normal. The heart was somewhat enlarged. Blood urea nitrogen 149 mgm. per cent. Blood creatinine, 2.0 mgm. per cent on admission, rose during 3 weeks to 4.9 mgm.

During observation the number of erythrocytes, leucocytes and casts in the urine decreased very much, but a few of each were still present 5 months after admission. The blood urea nitrogen and creatinine became normal about 3 months after admission. Patient returned to work as chauffeur, and refused to come back to hospital for subsequent examinations.

Case 15. Hospital No. 5441, F. C., male (colored), 25 years. *Hemorrhagic Bright's disease.* Acute → latent.

Five years before admission he had primary syphilis. He never had any secondary or tertiary symptoms. For 5 weeks before admission he had had bronchitis and for four and a half weeks edema.

On admission the urine sediment contained some erythrocytes, a few leucocytes, and many granular casts. The heart was not enlarged. Wassermann reaction was strongly positive. Blood urea nitrogen 21 mgm. per cent and blood creatinine 1.30 mgm. per cent. The basal metabolic rate was −6.1 per cent.

During observation the erythrocytes disappeared from the urine sediment, and the number of casts decreased. Blood pressure, blood urea nitrogen, and creatinine remained normal. The last 4 weeks of observation the patient had daily inunctions of mercury. He reported himself in good health two and one-half years after admission; consequently it is probable that his nephritis had either healed or become latent. He could not return for examination.

Case 16. Hospital No. 6538. J. Y., female, 25 years. *Hemorrhagic Bright's disease.* Acute → latent.

No history of previous infections. Eight months before admission hematuria had appeared, followed by edema. Hematuria had disappeared in two months, and edema had become more pronounced.

On admission pitting edema of the lower extremities was present. A 12-hour concentrated specimen of urine showed 1,900,000 red blood cells, 3,000,000 white blood and epithelial cells, and 125,000 hyaline casts. The protein excretion in the urine was 3.5 gram daily. The blood urea N was 17 mgm. per cent. The phenolsulfonephthalein test revealed a 54 per cent return of the dye in two hours.

During the 8 months that the patient was under observation the blood pressure remained normal. The phthalein excretion rose to above 60 per cent in 2 hours and remained above that level. In concentrated 12-hour specimens the urine sediment showed a variation in red blood cells between 150,000 and 2,860,000, the white blood cells and epithelial cells between 1,500,000 and 4,000,000, and the hyaline casts between 60,000 and 250,000. The protein excretion diminished to 0.5 gram daily at the end of the observation period. At no time was the blood urea nitrogen above 17 mgm. per cent.

Case 17. Hospital No. 5482. R. G., male, 11 to 12 years. *Hemorrhagic Bright's disease.* Acute → active chronic.

Two years before admission he had mastoiditis. He was operated on and a draining sinus remained. Three weeks before admission edema appeared and albumin and casts were found in the urine.

On admission the open pus-secreting mastoid process lesion was seen. The urine sediment contained many erythrocytes, some leucocytes and hyaline and granular casts and a few erythrocyte casts and doubly refractive bodies. The eyegrounds were normal. The heart was not enlarged. Blood urea nitrogen 29 mgm. per cent and blood creatinine 1.24 mgm. per cent. During the second month in hospital a secondary mastoid operation was done, and satisfactory healing occurred.

During observation there was no significant change in the urine sediment, plasma proteins, blood urea nitrogen or creatinine. The case was evidently an active chronic one when discharged 18 months after first observation.

Case 18. Hospital No. 5316. A. C., female, 27 years. *Hemorrhagic Bright's disease.* Acute → active chronic.

Five weeks before admission edema appeared and albuminuria was found.

On admission chronic tonsillitis was found. The urine sediment contained many erythrocytes, a few leucocytes and some hyaline and granular casts. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 20 mgm. per cent, blood creatinine 1.36 mgm. per cent and the basal metabolic rate −9.5 per cent.

Some time after admission a bleeding urethral polyp was found. It was removed by operation 5 months after admission. Erythrocyte casts were recorded twice. The urine sediment did not change significantly; occasionally doubly refractive bodies were found. The blood pressure remained normal. The blood urea nitrogen and creatinine increased slowly; 13 months after admission they were 36 and 2.08 mgm. per cent respectively.

Case 19. Hospital No. 4423. M. A., female, 16 to 20 years. *Hemorrhagic Bright's disease.* Acute → terminal → exitus.

Two months before admission albuminuria was accidentally found, and shortly afterwards edema appeared.

On admission an abscess of the right gum and several badly decayed teeth were found. The urine sediment contained many erythrocytes, few leucocytes, and many granular and a few erythrocyte casts. The eyegrounds were normal. Wassermann reaction was negative. Blood urea nitrogen was 28 mg. per cent and plasma cholesterol 255 mg. per cent.

During the 3½ years observation the blood urea nitrogen and creatinine gradually rose. After 2 years they were 89 and 3.2 mgm.; after 3 years 253 and 6.0 mgm. and 12 days before death they were 328 and 8.1 mgm. per 100 cc. respectively.

Death occurred in uremia and cardiac failure. The autopsy showed cardiac hypertrophy and contracted kidneys with extensive chronic hemorrhagic Bright's disease.

Case 20. Hospital No. 4911 and 5386. S. J., female (colored), 35 years. *Hemorrhagic Bright's disease.* Acute → active chronic → terminal → death.

Two months before admission edema appeared.

On admission the urine sediment contained some leucocytes, occasional erythrocytes and many hyaline and granular casts. The eyegrounds were normal. The heart was not enlarged. Blood urea nitrogen was 9 mgm. per cent. Thirteen months after admission the basal metabolic rate was −6.0 per cent.

During observation the blood urea nitrogen increased gradually and was 132 mgm. per cent two weeks before death, which occurred in uremia.

Autopsy. No. 249/1926. Autopsy commenced 9 hours after death.

Death in uremia. Cardiac hypertrophy. Small fresh areas of bronchopneumonia. Old adherent pleurisy and pericarditis. Old perisplenitis and perihepatitis. Ascites. Chronic cholelithiasis. Slight arteriosclerosis of the spleen. Slight atheromatosis of the aorta.

The right kidney weighed 165, the left 220 grams. The capsule stripped with difficulty. Both kidneys were firm. Their surface was very finely granulated and pale in color. Hemorrhages were absent. The cortex was of about normal width and pale in color. The differentiation of cortex and medulla was not sharp. The right kidney contained at the upper pole a cyst the size of an acorn.

Microscopic examination. All glomeruli are more or less diseased (fig. 1). Their loops are changed mostly into thick hyaline or protoplasmatic masses the lumina of which frequently can no longer be recognized (fig. 2). Part of the glomeruli show increased numbers of nuclei and are poor in erythrocytes. Occasionally one finds small necroses of the loops (fig. 2). Hemorrhages in the capsular spaces were not seen. Nearly all glomeruli are adherent to the capsules, often to a large extent. The capsules are mostly rich in nuclei and thickened by masses stained red by Van Gieson. Frequently one sees crescents rich in nuclei. The parietal epithelial cells are often increased in number and size. Fairly many glomeruli are entirely hyalinized.

The parenchyma is much destroyed (fig. 1) and penetrated by scars which are rich in collagenous connective tissue and in capillaries dilated with blood. Frequently they contain round cell infiltrations and occasionally polymorphonuclear leucocytes, which may enter the tubules. Xanthoma like cells were not seen. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. Between the scars one sees islands of better preserved tubules which are much dilated. They contain coagulated protein, some desquamated epithelial cells, some casts and in some places many polymorphonuclear leucocytes (fig. 1). Occasionally one sees calcified casts. The epithelial cells are mostly flattened. In single tubules one sees also hyaline-droplet degeneration. Occasionally one finds distinct signs of regeneration.

Some arterioli show an endarteritis. The larger arteries show a well developed intimal hyperplasia. The medulla is rich in collagenous connective tissue. In some places it contains scars rich in capillaries dilated with blood. The tubules are frequently atrophic or degenerated and contain an exudate similar to that of the cortex.

Anatomical diagnosis. Chronic glomerulonephritis. Secondary arteriosclerosis.

Case 21. Hospital No. 5254. M. M., female, 19 years. *Hemorrhagic Bright's disease.* Acute → death from diphtheria.

For some years she has had frequent colds. One week before admission edema appeared.

On admission the urine sediment contained some erythrocytes, leucocytes and granular casts and a few hyaline casts. The eyegrounds were normal. The heart was not enlarged. Wassermann reaction was negative. Blood urea nitrogen 26 mgm. per cent. Blood creatinine 1.58 mgm. per cent.

During observation the number of casts increased somewhat. The blood urea nitrogen during the first 4 months was about 35 mgm. per cent and was 80 mgm. per cent 11 months after admission. The blood creatinine at this time was 3.64 mgm. per cent. Eleven months after admission the patient died at home from diphtheria. No autopsy.

Case 22. Hospital No. 6029. M. K., female, 24 years. *Hemorrhagic Bright's disease.* Acute → uremic death.

Five weeks before admission she had diarrhoea and vomiting. One week later edema was called to her attention.

On admission considerable gingivitis was found. The urine sediment contained some erythrocytes, leucocytes, doubly refractive bodies, and hyaline and granular casts. The heart was somewhat enlarged. Wassermann reaction was negative. Blood urea nitrogen 58 mgm. per cent. Blood creatinine 1.76 mgm. per cent.

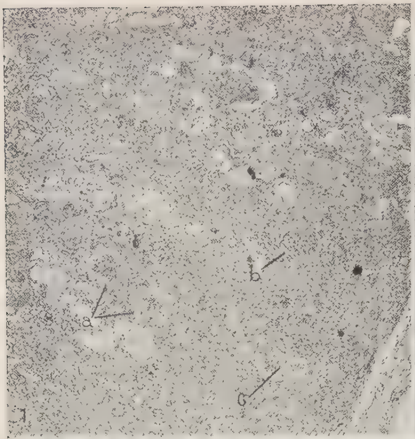
During observation vomiting and nausea were present. The number of casts increased, and some of these were broad (Addis' renal failure casts). The blood urea nitrogen rose to 170 mgm. per cent and blood creatinine to 2.67 mgm. per cent. The patient then contracted atypical pneumonia, caused by Type IV pneumococcus. One day before death the blood urea nitrogen was 418 mgm. per cent and blood creatinine 4.54 mgm. per cent. The autopsy showed pneumonia, pancreatic fat necrosis, cardiac hypertrophy, large mottled kidneys, with extensive hyaline degeneration of the glomeruli and in some places crescent formation. There was tubular atrophy and degeneration.

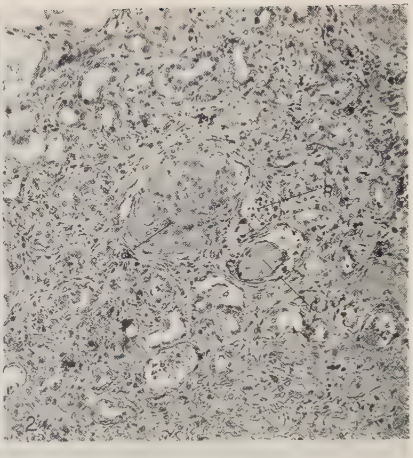
Autopsy. Autopsy No. 281/1927. Autopsy commenced 3 hours after death.

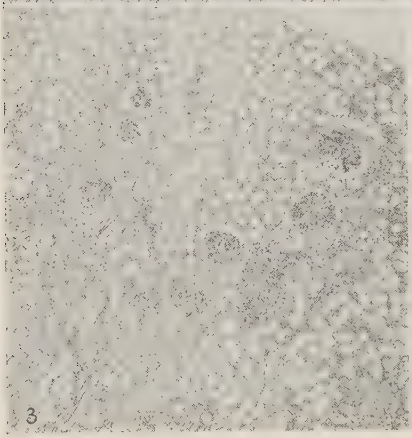
Death by confluent bronchopneumonia. Empyema of the right pleural cavity. Moderate cardiac hypertrophy. Serous pericarditis and ascites. Fibrinous perisplenitis. Old healed endocarditis mitralis. Moderate atheromatosis of the aorta, aortic cusp of the mitral valve and of the coronary arteries.

The right kidney weighed about 200, the left 210 grams. The capsule stripped easily. Both kidneys were doughy in consistency. In each kidney the surface was relatively smooth with very fine, slight granulations. It was yellowish white in color and contained occasional red dots. The cortex was a little enlarged and in color similar to the surface. Fine radiate brownish stripes were visible in it. The cortex was fairly well marked off from the brown red medulla.

Microscopic examination. All glomeruli are more or less severely changed (fig. 3). Their tufts are partly or entirely changed into thick hyaline or fibrinoid masses which are in part stained blue by Gram (fig. 4). The nuclei







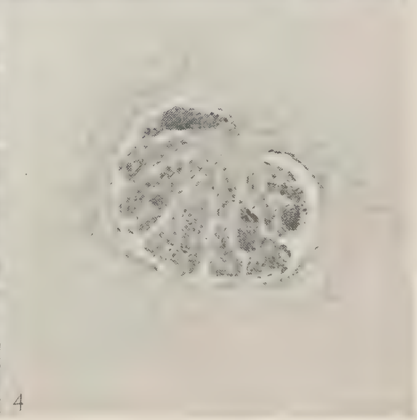


Fig. 1. Case 20. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

The tufts of the glomeruli are clotted with hyaline and protoplasmic masses and are frequently adherent to the capsules. Some of the capsules are much thickened (*a*). The covering cells of the tufts are increased in number (*b*). The parenchyma is greatly destroyed and penetrated by scars which contain round cell infiltrations. The remaining tubules contain coagulated protein, polymorphonuclear leucocytes, (*c*), and occasionally calcified casts. Zenkers, iron-hematoxylin-eosin. ×60.

Fig. 2. Case 20. For diagnosis see figure 1.

The tuft of the glomerulus is changed into thick protoplasmic and hyaline masses the lumina of which can no longer be recognized. In (*a*) one sees a small necrosis. The tuft is adherent to the capsule in many places. The capsule is thickened. In the surrounding tubules and interstitial tissue one sees some polymorphonuclear leucocytesr (*b*). In (*c*) desquamated epithelial cells and cellular detritus in a tubule. Zenkers, iron-hematoxylin. ×200.

Fig. 3. Case 22. Anatomical diagnosis: subacute glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis developed directly from acute.

The glomeruli are enlarged and rich in endothelial cells and polymorphonuclear leucocytes. Part of their loops are necrotic and fibrinoid or hyaline. In a few places one sees adhesions of the tufts to the capsules. The tubules contain coagulated protein and some polymorphonuclear leucocytes. In the interstitial tissue a few scars with infiltrations of round cells and a few polymorphonuclear leucocytes. Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

Fig. 4. Case 22. For diagnosis see figure 3.

The loops of the glomerulus are clotted with fibrinoid masses and are adherent to the capsule. Mueller-formalin fixation, Gram. ×200.

of such tufts are often necrotic and bizarrely shaped. Other parts of these glomeruli contain *greatly increased numbers of nuclei* (fig. 3) partly of proliferated endothelial cells and partly of polymorphonuclear leucocytes. Occasionally one sees karyokinetic figures. The tufts are thrombosed in some instances. Part of the glomeruli are enlarged. Their tufts extend frequently into the tubules like hernias. They are extremely poor in erythrocytes. In some instances one sees adhesions of the tufts to the capsules. In the glomerular spaces one sees a little coagulated protein and detritus. The capsules are well preserved in most instances. Occasionally the parietal epithelial cells are increased in number. A few capsules are thickened by masses stained red by Van Gieson. Relatively frequently one sees also crescents which occasionally are very thick and consist of several layers, rich in nuclei. These changes are, however, insignificant in contrast to the intracapillary changes. Several glomeruli are entirely hyalinized. The more severely changed glomeruli contain in part much fat which occasionally is doubly refractive.

The parenchyma is penetrated by a few scars which are rich in collagenous connective tissue and capillaries dilated with blood. Frequently they contain round cell infiltrations. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. The better preserved tubules are frequently dilated and contain varying amounts of coagulated protein, polymorphonuclear leucocytes and desquamated epithelial cells. Occasionally they contain hyaline casts. The epithelial cell of the ascending loops are swollen in part and frequently fatty degenerated. Hyaline-droplet degeneration is rare and insignificant. In some places one sees signs of regeneration.

The arterioli are mostly well preserved. Occasionally they show a moderate endarteritis. The larger arteries show a moderate intimal hyperplasia.

Anatomical diagnosis. Subacute glomerulonephritis. Intracapillary form of Fahr.

Case 23. Hospital No. 6112. F. S., male, 44 years. *Hemorrhagic Bright's disease.* Acute → terminal → exitus.

The patient 2 years before admission had been told that his urine contained no albumin and that his blood pressure was normal. Four months prior to coming to hospital, he had contracted a severe cold which had been followed by arthritis. There had been no gross hematuria or edema.

On admission the patient was in an uremic condition. There was severe anemia. The hemoglobin was 8.8 volume per cent O_2 capacity. There was no edema. The heart was not enlarged. The urine contained a quantity of albumin, red blood cells, white blood cells, and casts. Many of the casts were of the broad renal failure type (Addis, 1925). The blood urea N was 117 mgm. per cent, the creatinine 9.9 mgm. per cent. The phthalein output was but 2 per cent in 2 hours.

During the 2 months that the patient was under observation, the blood urea N remained between 91 and 117 mgm. per cent. The creatinine stayed at 9 mgm. per cent. The phthalein excretion was reduced during the second month to a trace in two hours. The hemoglobin was constant at 8 volumes per cent O_2 capacity. The excretion of albumin, red blood cells and casts continued. Slight edema appeared a few days before death. There was a slight elevation of the systolic blood pressure level during the last month,—the diastolic level remained normal. The patient died in uremic coma.

Autopsy. Autopsy No. 283/1927. Autopsy commenced 3 hours after death.

Death by bronchopneumonia. Fresh serous fibrinous pleurisy. Old adherent pleurisy of the left cavity. Serous pericarditis Ascites. Old adherent perisplenitis and perihepatitis. Old healed endocarditis. Old infarcts in the spleen. Moderate atheromatosis of the aortic cusp of the mitral valve, of the coronary arteries and of the aorta.

Neither the right kidney nor its ureter and arteries could be found. The left kidney was very large. Length 16, breadth 8 cm. The capsule stripped with difficulty. The kidney was doughy in consistency. Its surface was smooth and occasionally slightly granulated. It was yellowish white in color showing red blood dots. The cortex was much enlarged showing a picture similar to that of the surface. The cortex was well marked off from the medulla.

Microscopic examination. All glomeruli are severely diseased (fig. 5). Their tufts are entirely clotted by hyaline masses (fig. 6) stained red by Van Gieson in most instances. Nearly all glomeruli are empty of blood and show partially increased numbers of nuclei. Occasionally one sees necroses of the loops. Nearly all glomeruli are adherent to the capsules to a large extent (fig. 5). In the capsular spaces one finds some coagulated protein and erythrocytes in places. The covering cells of the glomeruli as well as the parietal epithelial cells are much increased in number and show *frequently typical crescents* (fig. 6). The capsules are thickened and cannot be sharply differentiated from the surrounding tissue.

The tubules are frequently dilated and contain some coagulated protein, casts, some erythrocytes and polymorphonuclear leucocytes. Their epithelial cells are much desquamated. Some are flattened. Others are swollen and occasionally show hyalin-droplet degeneration. The interstitial tissue is thickened in some instances and contains round cellular infiltrations (fig. 6). The arterioli are relatively well preserved. The larger arteries show a slight intimal hyperplasia.

Histological diagnosis. Subacute glomerulonephritis. Extracapillary form of Fahr. Aplasia of the right kidney.

.*Case 23a.* Hospital No. 5227. G. G., male, 24 years. *Hemorrhagic Bright's disease.* Latent → terminal.

The patient had a heavy cold a year before admission. He first noted edema about the ankles 5 months later, and albumin was discovered in the urine. Examination disclosed nothing abnormal beyond a low grade of chronic tonsillitis, and slight edema. The heart was normal in size. The urine contained about 4 grams of albumin per day. There were many hyaline casts, and some granular casts in the sediment. A few red and a few white blood cells were occasionally noted, and fatty epithelial cells. Blood urea N was 12 mgm. per cent. Blood creatinine 1.64 mgm. per cent. Plasma cholesterol 217 mgm. per cent.

The edema cleared up quickly, and did not recur until 2 years later. There has been a definite downward progress in renal function during the last 2 years, and marked hypertension, 175/125, and hematuria have developed. The case is apparently passing from the latent stage, where it resembled a mild nephrosis, into the terminal stage of hemorrhagic nephritis.

Case 24. Hospital No. 5058. I. R., male, 37 years. *Hemorrhagic Bright's disease.* Latent → terminal → exitus.

Nine years before admission he had acute nephritis. One year later he had a relapse, and this time gross hematuria was noticed. Since then albuminuria has persisted. He never noticed any edema.

On admission pyorrhea alveolaris and chronic bronchitis were found. The urine sediment contained a few erythrocytes and some hyaline and granular casts. The eyegrounds were normal. The heart size was normal. Blood urea nitrogen was 53 mgm. per cent, blood creatinine 2.0 mgm. per cent and the basal metabolic rate +1.8 per cent.

The pyorrhea improved after treatment. Twenty-five nonths after admission headaches, nausea and hypertension were present. Blood urea nitrogen was 102 mgm. per cent and blood creatinine 2.75 mgm. per cent. Thirty-four months after admission retinal hemorrhages were present, and the heart was enlarged. The blood urea nitrogen was 291 mgm. per cent and blood creatinine 14.4 mgm. per cent. The maximal values reached were

910 mgm. per cent and 20.32 mgm. per cent respectively. Patient died in uremia. No autopsy.

Case 25. Hospital No. 5446. R. V., male, 25 years. *Hemorrhagic Bright's disease.* Active chronic → terminal.

He has had rather frequent colds. Five months before admission after a severe cold edema and dyspnoea appeared. One month later tonsillectomy was performed.

On admission there was no dyspnoea. Large adenoids and remnants of tonsillar tissue with foci of pus were present. The urine sediment contained many erythrocytes, leucocytes, and hyaline and granular casts, also some cellular casts and doubly refractive bodies. The eyegrounds were normal. The heart was somewhat enlarged. Wassermann reaction was negative. Blood urea nitrogen 39 mgm. per cent. Blood creatinine 2.13 mgm. per cent. Six months after admission the basal metabolic rate was +6.6 per cent. Nine months after admission, the adenoids and tonsillar tags were removed. No improvement occurred after the operation, nor did the urine sediment and blood pressure at the time change significantly. Twelve months after admission the blood urea nitrogen was 69 mgm. per cent and the blood creatinine 3.70 mgm. per cent. The patient was then up and about and working 6 hours each day, despite the progressive decrease of renal function.

Case 26. Hospital No. 6139. A. P., male, 19 years. *Hemorrhagic Bright's disease.* Active chronic.

The patient had chronic tonsillitis for many years. Eight months before admission edema appeared, and one month later albuminuria, hematuria and hypertension were found. All these signs were present when he was admitted to this hospital.

On admission the urine sediment contained many erythrocytes, some leucocytes and hyaline casts, many erythrocyte casts and occasional doubly refractive bodies. The eyegrounds were normal. Chronic tonsillitis was found. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 35 mgm. per cent. Blood creatinine 1.86 mgm. per cent. The tonsils and adenoids were removed, without any subsequent flare up in the Bright's disease. A month later, he was allowed up, and an increase in hematuria occurred, lasting about a week.

Case 27. Hospital No. 5074. M. G., male, 11 to 13 years. Height 138.5 to 145.5 cm. *Hemorrhagic Bright's disease.* Active chronic → terminal.

He had pneumonia at 6, 7 and 10 years of age. After the last attack, 18 months before admission, edema and ascites appeared and albuminuria was found.

On admission chronic tonsillitis and chronic bronchitis were found. The urine sediment contained occasional erythrocytes and granular casts. The heart was somewhat enlarged. Wassermann reaction was negative. Blood urea nitrogen 18 mgm. per cent. Blood creatinine 1.48 mgm. per cent. Basal metabolic rate +3.6 per cent.

Fourteen months after admission the urine sediment contained many erythrocytes and granular and cellular casts and a few leucocytes, and these findings have persisted. On several occasions some doubly refractive bodies have also been found. The blood pressure most of the time has been about 140/80. Intermittent chronic bronchitis has persisted. Twenty-four months after admission chronic frontal and ethmoidal sinusitis appeared, caused by hemolytic streptococcus. The blood urea nitrogen has been about 60 mgm. per cent most of the time and the blood creatinine about 1.80 mgm. per cent. The plasma proteins have not changed significantly. He was still able to be active over 6 years after the onset of his disease, and a year and a half since it has been in the terminal stage. In that time, however, his blood urea clearance has sunk from 20 to 12 per cent of normal.

Case 28. Hospital No. 6123. L. G., female, 19 years. *Hemorrhagic Bright's disease.* Active chronic → terminal.

Six months before admission edema appeared. One month later marked albuminuria and hematuria were found. At the Lenox Hill hospital the basal metabolic rate was found to be −32 per cent and the plasma cholesterol 375 mgm. per cent.

On admission here the urine sediment contained some erythrocytes, leucocytes and hyaline and granular casts. The eyegrounds were normal. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 71 mgm. per cent. Creatinine 1.33 mgm. per cent. Plasma proteins were low and edema general, with ascites. Four months after admission the plasma cholesterol was found to be 1113 mgm. per cent. During observation no significant change was found in the urine sediment.

Case 29. Hospital No. 5210. P. L., male, 28 years. *Hemorrhagic Bright's disease.* Active chronic → terminal.

Seven months before admission moderate edema gradually appeared.

On admission abscesses were found at the roots of two teeth. The urine sediment contained some erythrocytes and leucocytes and hyaline, epithelial and granular casts. The eyegrounds were normal. The heart size was normal. Wassermann reaction was negative. Blood urea nitrogen 44 mgm. per cent. Blood creatinine 1.62 mgm. per cent.

Plasma albumin increased gradually until it approached normal levels. The urine sediment did not change much except for the appearance of broad casts 25 months after admission. Sixteen months after admission a gradual rise began in the blood urea nitrogen and creatinine. Thirty-four months after admission they were 213 mgm. per cent and 8.58 per cent respectively, blood urea clearance 12 per cent of normal. Lobar pneumonia occurred 29 months after admission caused by pneumococcus Type III. He made a good recovery. When seen 41 months after his first admission, he had no complaints, his blood urea clearance was still 12 per cent of normal, and his general appearance was very good. He had then been 7 months at home unrestricted with regard to activity and diet.

Case 30. Hospital No. 5699. N. J., male, 23 years. *Hemorrhagic Bright's disease.* Active chronic → terminal.

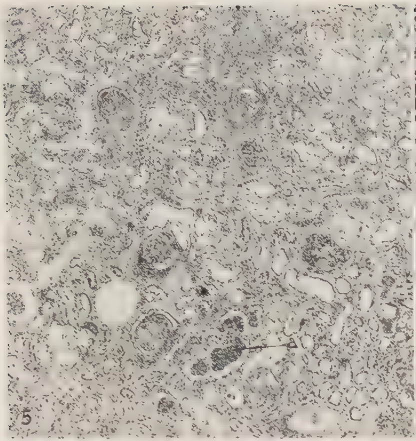
The last 3 years before admission he had several attacks of tonsillitis. After such an attack 15 months before admission edema appeared and albuminuria was found. The condition improved under treatment, but the patient developed psoriasis, for which he was treated with chrysarobin. Two days later the edema reappeared and was present until admission. Three months before admission tonsillectomy was performed. After this the systolic blood pressure rose gradually from normal to 145 mm.

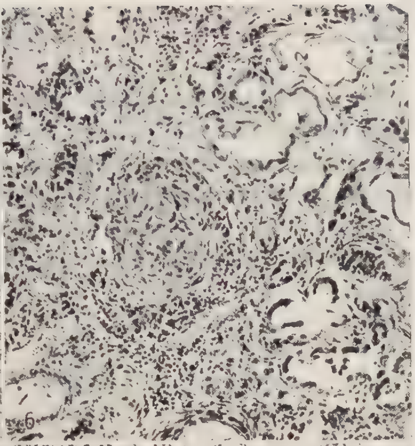
On admission some patches of psoriasis were present. The urine sediment contained some erythrocytes, a few leucocytes and hyaline casts, and many granular casts. The eyegrounds were normal, the blood pressure about 135/90, the heart somewhat enlarged to the left. Wassermann reaction was negative. Blood urea nitrogen 23 mgm. per cent. Blood creatinine 1.93 mgm. per cent.

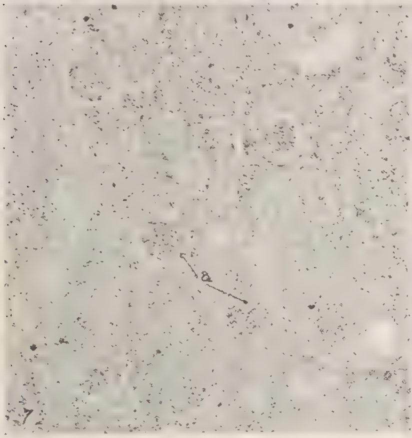
The edema and psoriasis disappeared rapidly. Since 2 months after admission the patient has been able to do clerical work. Twenty months after admission he had begun to suffer from attacks of headache and vomiting, and the blood pressure had then increased to 188/126.

Case 31. Hospital No. 4212. H. M., male, 5 to 10 years. Height 105 to 120 cm. *Hemorrhagic Bright's disease.* Active chronic → terminal → exitus.

One brother of the mother died of acute uremia and another had acute hemorrhagic nephritis.







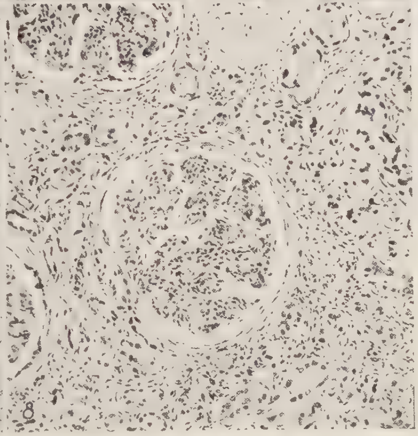


Fig. 5. Case 23. Anatomical diagnosis: subacute glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis developing directly from acute.

The tufts of the glomeruli are clotted with hyaline masses. The covering cells of the tufts as well as the parietal epithelial cells are greatly increased in number forming crescents. The tubules are degenerated and, in a few places, contain polymorphonuclear leucocytes (*a*). Zenkers, iron-hematoxylin-eosin. ×60.

Fig. 6. Case 23. For diagnosis see figure 5.

The tuft of the glomerulus is clotted with hyaline masses and empty of blood. The endothelial cells are necrotic in part. The glomerular space is filled by a large crescent consisting of granulation tissue. The interstitial tissue is infiltrated by round cells. Zenkers, iron-hematoxylin-eosin. ×200.

Fig. 7. Case 34. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

Some glomeruli are enlarged and rich in endothelial cells and polymorphonuclear leucocytes. Some of the tufts are clotted and, in a few places adherent to the capsules (*a*). Other glomeruli are entirely hyalinized. The tubules are in all stages of atrophy and degeneration. The interstitial tissue is thickened. Zenkers, iron-hematoxylin-eosin. ×60.

Fig. 8. Case 34. For diagnosis see figure 7.

The glomerulus is enlarged and rich in endothelial cells and polymorphonuclear leucocytes. The loops are clotted and, in one place adherent to the capsule. Zenkers, iron-hematoxylin-eosin. ×200.

Six months before admission edema appeared and albuminuria was found. Both have persisted.

On admission chronic tonsillitis was found. The urine sediment contained few erythrocytes and many granular casts. The eyegrounds were normal. The heart was not enlarged. Wassermann reaction was negative. Blood urea nitrogen 52 mgm. per cent. Plasma cholesterol 780 mgm. per cent.

Between the 54th and 60th months after admission blood creatinine rose from 2.1 to 3.7 mgm. per cent and blood urea N from 67 to 234 mgm. per cent. Two days before death in uremia the figures had risen to 17.0 and 403 mgm. respectively. No autopsy.

Case 32. Hospital No. 5068. J. S., male, 15 years. Height 176 cm. ideal weight 61.3 kgm. F = 0.99. *Hemorrhagic Bright's disease.* Active chronic → terminal → exitus.

Two years before admission he had scarlet fever followed by acute nephritis with hematuria, hypertension and edema. Since then persistent albuminuria and intermittent edema have been present.

On admission the urine sediment contains very few hyaline and granular casts. The heart size was normal. Blood urea nitrogen 20 mgm. per cent. Basal metabolic rate +3.2 per cent.

During observation the number of casts increased. At the terminal stage broad casts are present. The systolic blood pressure rose steadily and reached 202/76 before death. The diastolic pressure was never found to be increased. Enlargement of the heart was first noticed 17 months after admission. The blood urea nitrogen and creatinine increased gradually and were 341 and 10.7 mgm. per cent respectively, 4 days before death. Plasma albumin oscillated between 2.32 and 3.08 per cent. No definite signs of uremia were present before death. No autopsy.

Case 33. Hospital No. 5082. J. L., male, 16 to 20 years. *Hemorrhagic Bright's disease.* Active chronic → terminal → exitus.

Three months before admission edema appeared and albuminuria was found.

On admission adenoid hypertrophy was found. The urine sediment contained some erythrocytes and leucocytes and hyaline, granular, and cellular casts. The eyegrounds were normal. The heart size normal. Wassermann reaction was negative. Blood urea nitrogen 47 mgm. per cent. Creatinine 1.51 mgm. per cent. Plasma cholesterol was 457 mgm. per cent two months after admission. Thirty-nine months after admission the patient returned to hospital, complaining of weakness, vomiting and itching. He died 8 days later, from uremia, and a septicemia due to streptococcus hemolyticus. No autopsy.

Case 34. Hospital No. 4410 and 5055. S. L., male, 18 to 20 years. *Hemorrhagic Bright's disease.* Active chronic → terminal → exitus.

Four months before admission edema appeared and albuminuria was found. One month later hypertension was found.

On admission the urine sediment contained some erythrocytes, leucocytes, and erythrocyte casts, and many hyaline and granular casts. The eyegrounds show papillary edema and a few spots of exudate. The heart was somewhat enlarged. Blood urea nitrogen 30 mgm. per cent. Plasma cholesterol 715 mgm. per cent.

During observation the urine sediment did not change significantly except for the number of erythrocytes present. Twenty-six months after admission blood urea nitrogen was 160 mgm. per cent and creatinine 5.7 mgm. per cent. Thirty-four months after admission blood urea nitrogen was 340 mgm. per cent and creatinine 20.3 mgm. per cent.

Autopsy. Autopsy. No. 215/1924. Autopsy commenced 13 hours after death.

Death in uremia. Cardiac hypertrophy. Small fresh areas of bronchopneumonia. Serous fibrinous pericarditis. Serous fibrinous adhesive pleurisy. Ascites. Arteriosclerosis of the spleen. Moderate atheromatosis of the aortic cusp of the mitral valve, and of the coronary arteries. Advanced atherosclerosis of the aorta.

Each kidney weighed 125 grams. The capsule stripped very readily. The surface was pale grayish in color and finely and coarsely granulated. Hemorrhages have not been recorded. The cortex was much narrowed and pale yellowish in color. The differentiation of cortex and medulla was obvious.

Microscopic examination. All glomeruli are more or less severely diseased (fig. 7). They vary in size and are often very large. Mostly they are *very rich in nuclei* (fig. 8), partly with increased numbers of endothelial cells, partly with accumulation of polymorphonuclear leucocytes. Frequently the tufts are thickened by protoplasmatic or hyaline masses so that the lumina can no more be recognized. Most glomeruli are poor in erythrocytes. But single glomeruli or loops are dilated with blood. Single glomeruli are necrotic. Frequently, the glomeruli contain much fat which in part is doubly refractive. The capsular spaces occasionally contain blood. Some glomeruli are adherent to the capsules. The capsules are mostly thickened by masses stained reddish yellow by Van Gieson. The capsular epithelial cells are increased in number in some instances. Occasionally one finds thick crescents rich in nuclei. Many glomeruli are entirely hyalinized (fig. 7).

The parenchyma is penetrated by many scars which are rich in collagenous connective tissue and capillaries dilated with blood. Round cell infiltrations are frequent. Interstitial xanthoma-like cells have not been found. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. Part of them have undergone fatty degeneration. The better preserved tubules are dilated in part and contain coagulated protein, cellular detritus, some casts and desquamated epithelial cells. In some places they contain also some polymorphonuclear leucocytes. Part of their epithelial cells contain fat which may be doubly refractive. Hyaline-droplet degeneration has not been found.

Some arterioli show a distinct endarteritis. Frequently they contain fat. The larger arteries show a moderate intimal hyperplasia. The medulla contains scars rich in collagenous connective tissue and capillaries dilated with blood. The medullary tubules are often atrophic or degenerated and filled by an exudate similar to that of the cortex.

Anatomical diagnosis. Secondary contracted kidneys. Chronic glomerulonephritis.

Case 35. Hospital No. 5409. M. K., female, 14 years. Height 149.5 cm. *Hemorrhagic Bright's disease.* Active chronic + pneumonia → terminal + empyema → exitus.

When 12 years old she had a severe cold followed by albuminuria, edema and ascites. After 6 weeks these symptoms disappeared but returned one month before admission after another cold.

On admission the urine sediment contained some erythrocytes, a few leucocytes and some hyaline and granular casts. The eyegrounds were normal, also the heart size. Wassermann reaction was negative. Blood urea nitrogen 27 mgm. per cent. Blood creatinine 1.30 mgm. per cent.

Three months after admission the patient had atypical pneumonia followed by empyema, both caused by hemolytic streptococci. Thoracotomy was performed. After that the amount of casts increased and the blood pressure rose to about 140/105. During the last month blood urea nitrogen rose to 178 mgm. per cent and bood creatinine to 8.0 mgm. per cent. Death occurred from emaciation and cardiac weakness. No autopsy.

Case 36. Hospital No. 5178. R. N., male, 38 years. *Hemorrhagic Bright's disease.* Active chronic → terminal → exitus.

Nine months before admission edema appeared and hypertension, albuminuria and hematuria were found.

On admission the urine sediment contained a few erythrocytes and some casts. The eyegrounds were normal. Chronic tonsillitis was found. The heart was slightly enlarged. Blood urea nitrogen 45 mgm. per cent. Blood creatinine 1.71 mgm. per cent. Basal metabolic rate −4.6 per cent.

Five months after admission tonsillectomy was performed. Four months later retinal hemorrhages and papillary edema and hypertension appeared. The urine sediment contained many hyaline, granular, and erythrocyte casts and a few doubly refractive bodies. Blood urea nitrogen was 53 mgm. per cent and blood creatinine 2.33 mgm. per cent.

During the next 4 months exudative albuminuric retinitis set in. Thirteen months after admission the blood pressure was 216/134, blood urea nitrogen 86 mgm. per cent and blood creatinine 4.29 mgm. per cent. Plasma albumin had now increased to 2.66 per cent. The last 3 months before death blood urea nitrogen rose to a maximum of 119 mgm. per cent, blood creatinine to 9.38 mgm. per cent. The urine sediment contained many broad granular renal failure casts (Addis, 1925). The death was cardiac in type. The autopsy showed cardiac hypertrophy, terminal hemorrhagic Bright's disease, and congestion of the organs.

Case 37. Hospital No. 5763. G. B., male, 56 years. *Hemorrhagic Bright's disease.* Chronic active → terminal → exitus.

Three months before admission slight edema appeared and the urine was found to contain a trace of albumin and a few hyaline cases. At the same time the systolic blood pressure was found to be 190 mm. Blood pressure determinations 8, 7 and ¾ years before admission had shown normal figures.

On admission the urine sediment contained many erythrocytes and some leucocytes and hyaline, granular and erythrocyte casts. The heart size was normal. Blood urea nitrogen 27 mgm. per cent. Blood creatinine 2.10 mgm. per cent.

During observation the number of granular casts was increased somewhat. One week before death blood urea nitrogen was 300 mgm. per cent. Death occurred in uremia.

Autopsy. Autopsy No. 293/1928. Autopsy commenced 22 hours after death.

Death in uremia. Uremic hemorrhages in the intestine. Cardiac hypertrophy. Fresh bronchitis with small bronchopneumonic areas. Serofibrinous pleurisy. Serous pericariditis. Arteriosclerosis of the spleen. Moderate atheromatosis of the aortic cusp of the mitral valve, of the coronary arteries and of the aorta.

The right kidney weighed 70, the left 60 grams. The capsule stripped with difficulty. The kidneys were firm. Their surfaces were grayish in color and finely and coarsely granulated. Blood dots were not seen. The cortex was much narrowed and yellowish gray in color. It was fairly well marked off from the medulla which was striped brown and yellowish.

Microscopic examination. Nearly all glomeruli are more or less altered (fig. 9). One-third of them are entirely hyalinized. Most of the rest are of usual size, but part are enlarged. Most of *their tufts are much clotted* and can no longer be differentiated distinctly (fig. 10). Most of them contain few or no erythrocytes. Frequently, they contain increased numbers of nuclei. Necroses of the loops are rare. In a few glomeruli one finds hemorrhages. The glomeruli are frequently adherent to the capsules. These are frequently thickened by masses stained red by Van Gieson. In a few places one sees proliferations of the parietal epithelial cells. In some instances one sees even crescents, some of which show spaces filled with blood between the layers. But these changes are insignificant in contrast to the intracapillary ones. Occasionally, the glomeruli contain a little fat.

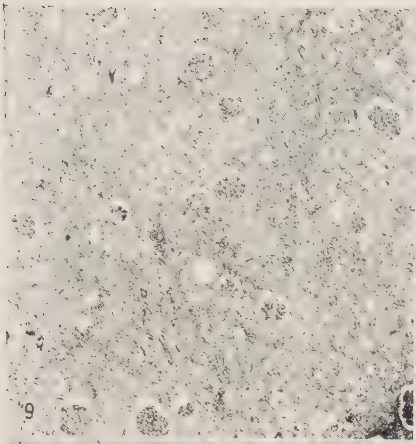
The parenchyma of the kidneys is much destroyed and penetrated by scars between which preserved and dilated tubules stand out like islands. The tubules are found in all stages of atrophy and degeneration. Their epithelial cells are mostly flattened and frequently show irregular fatty degeneration. Hyaline-droplet degeneration cannot be found. In the lumina of the tubules one sees some desquamated epithelial cells, a large amount of coagulated protein, and in a few places also polymorphonuclear leucocytes.

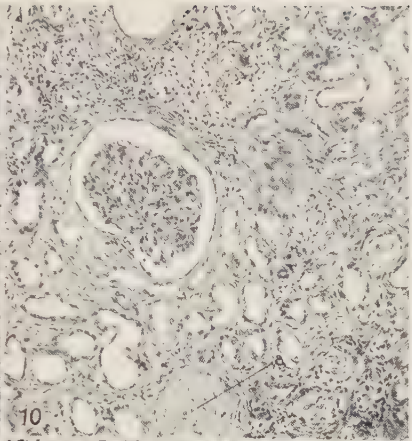
The interstitial tissue is often enlarged and rich in collagenous connective tissue and capillaries dilated with blood. In some places it contains infiltrations of round cells. Interstitial lipoid cells cannot be found. The arterioli are mostly well preserved. A few show endarteritis. A few also are hyalinized and contain fat. The larger arteries show an intimal hyperplasia.

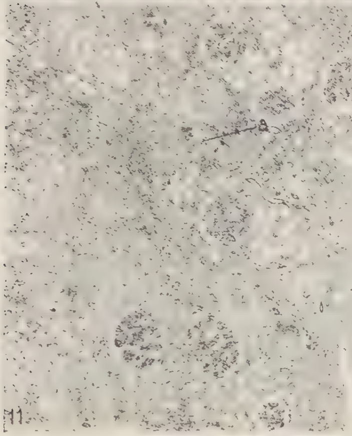
Anatomical diagnosis. Secondary contracted kidneys. Chronic glomerulonephritis. Secondary arteriosclerosis.

Case 38. Hospital No. 5340. E. S., female, 31 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

The patient has always been subject to sore throat. Eleven years before







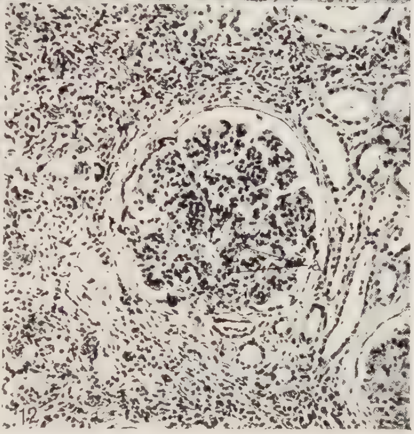


FIG. 9. Case 37. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

The loops of all glomeruli are clotted and can no longer be differentiated. Their nuclei are increased in number. Some glomeruli are entirely hyalinized. The tubules are in all stages of atrophy and degeneration. The interstitial tissue is rich in scars. Zenkers, iron-hematoxylin-eosin. ×60.

FIG. 10. Case 37. For diagnosis see figure 9.

The loops of the glomerulus are clotted with hyaline masses and can no longer be differentiated. They do not contain blood. The capsule is thickened. In (*a*) a hyalinized glomerulus Zenkers, iron-hematoxylin-eosin. ×200.

FIG. 11. Case 38. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

The glomeruli are greatly enlarged and rich in endothelial cells and polymorphonuclear leucocytes. Their tufts are clotted with hyaline and protoplasmic masses and frequently adherent to the capsules. In the glomerular spaces one sees some desquamated epithelial cells. Some glomeruli are entirely hyalinized The parenchyma contains scars, the tubules of which are in all stages of atrophy and degeneration. Between the scars one sees islands of enlarged tubules the epithelial cells of which have undergone fatty degeneration. The arterioli show a marked endarteritis (*a*). Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

FIG. 12. Case 38. For diagnosis see figure 11.

The glomerulus is enlarged and very rich in endothelial cells and polymorphonuclear leucocytes. The loops are clotted in places and adherent to the capsule. The parietal epithelial cells are increased in number. In (*a*) necrosis of a loop. The surrounding connective tissue is rich in round cells. Mueller-formalin fixation, iron-hematoxylin-eosin. ×200.

admission she had acute nephritis of one month's duration. Three years later edema occurred for the first time; it persisted most of the time until a few months before admission. The last year headache and dyspnoea appeared.

On admission the urine sediment contained a few erythrocytes, leucocytes and hyaline casts. The eyegrounds showed fresh hemorrhages and papillary edema. The heart was increased in size. Wassermann reaction was negative. Blood urea nitrogen 40 mgm. per cent. Blood creatinine 3.31 mgm. per cent. Basal metabolic rate +9.7 per cent.

Eleven months after admission the casts had practically disappeared from the urine, the blood urea nitrogen was 85 mgm. per cent and blood creatinine 4.81 mgm. per cent.

Twenty-four months after admission the blood urea nitrogen was 3.4 mgm. per cent and blood creatinine 16.35 mgm. per cent. Death occurred in uremia.

Autopsy. Autopsy No. 277/1927. Autopsy commenced 1½ hours after death.

Death in uremia. Uremic hemorrhages in the intestine. Cardiac hypertrophy. Fresh bronchitis and obliterative bronchiolitis. Fresh serofibrinous adherent pleurisy of the right cavity. Fresh serofibrinous pericarditis. Fresh perisplenitis and perihepatitis. Advanced arteriosclerosis of the spleen. Advanced atherosclerosis of the abdominal aorta, and of the coronary arteries. Moderate atheromatosis of the thoracic aorta and of the aortic cusp of the mitral valve.

The right kidney weighed 55, the left 65 grams. The capsule stripped with difficulty. Both kidneys were firm. Their surfaces were very finely granulated and grayish in color. Small hemorrhages were numerous. The cortex was much narrowed, yellowish gray in color and contained fine blood dots. It was not well marked off from the medulla.

Microscopic examination. All glomeruli are more or less severely damaged (fig. 11). They are of varying, frequently enormous, size and are in all stages of hyalinization up to entire hyaline change. Mostly they are *very rich in nuclei* (fig. 12), partly of proliferated endothelial cells and partly of polymorphonuclear leucocytes which are much increased in number. Their tufts are filled with hyaline or protoplasmatic masses. Most of them are poor in blood. But, in some instances, they contain capillaries well filled with erythrocytes. Some glomeruli are necrotic and contain blood within their spaces. Frequently, the glomeruli contain fat, part of which is doubly refractive. In the glomerular spaces one sees also coagulated protein. The glomeruli are mostly adherent to the capsules. The parietal epithelial cells are partly intact. In other places they are increased in number (fig. 12). Frequently one sees also crescent formations, but these changes are insignificant in contrast to the intracapillary changes. Many glomeruli are entirely hyalinized.

The parenchyma is penetrated by many scars which are rich in collagenous connective tissue and contain many round cell infiltrations. They are rich in capillaries dilated with blood, and contain a fair number of calcified areas and chains of xanthoma-like lipoid cells (fig. 13). Occasionally one sees polymorphonuclear leucocytes entering the tubules. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. Their epithelial cells contain often much fat, part of which is doubly refractive. Between the scars small islands of better preserved tubules are seen, the lumina of which contain coagulated protein, some desquamated epithelial cells, some casts, and occasionally also polymorphonuclear leucocytes. The epithelial cells of the ascending loops are in places swollen (fig. 11) and contain much fat. Hyaline-droplet degeneration is rare and insignificant.

The arterioli show often an endarteritis, partly of high degree (fig. 11), and occasionally necroses of their walls. Some arterioli are hyalinized and infiltrated with fat. The larger arteries show an advanced intimal hyperplasia and in a few places also calcification. Also the medulla contains many scars rich in round cell infiltrations and capillaries dilated with blood.

Anatomical diagnosis. Secondary contracted kidneys. Chronic glomerulonephritis. Secondary arteriosclerosis.

Case 39. Hospital No. 6215. H. B., male, 32 years. *Hemorrhagic Bright's disease.* Terminal, following 7 years latent → exitus.

The patient had had hematuria following exposure in trenches during the war, 10 years before admission. He had had edema at that time which persisted for five months. He was then told that there was a quantity of albumin in his urine. The patient had been symptom free during the following seven years. At the end of that period, or 3 years before admission to hospital, he had felt weak. He was told then that he had high blood pressure. Symptoms of headache, nocturia, and blurring of vision soon followed. Five weeks before admission hemorrhage from the gums had occurred, also a generalized body itch.

On admission to hospital, the patient was in uremia. Physical examination revealed signs of valvular disease of the heart, and cardiac enlargement. The blood pressure measured 193 mm. systolic and 124 mm. diastolic. The blood urea N was 138 mgm. per cent, and the plasma NPN 177 mgm. per cent. The phthalein excretion was but a trace in 2 hours. The urine contained 2 grams of albumin daily. Numerous red blood cells and Addis' failure casts were observed in the sediment.

During the few days that the patient was under observation, uremic symptoms became more aggravated. Broncho-pneumonia developed and hastened death.

Autopsy. No. 289/1927. Autopsy commenced 17 hours after death.

Death by confluent bronchopneumonia. Cardiac hypertrophy. Serofibrinous pleurisy and pericarditis. Cartilagenous perisplenitis. Old healed endocarditis. Advanced arteriosclerosis of the spleen. Advanced atherosclerosis of the coronary arteries. Moderate atheromatosis of the aortic cusp of the mitral valve and of the aorta.

The kidneys were extremely small. The right kidney weighed 50, the left 40 grams. The capsules stripped with difficulty. Both kidneys were firm. Their surfaces were finely granulated and yellowish gray in color, showing a number of small blood dots. The cortex in each was much narrowed and similar in color to the surface. The differentiation between cortex and medulla was indistinct.

Microscopic examination. Nearly all glomeruli are more or less diseased (fig. 14). Many glomeruli are hyalinized and stained yellowish red by Van Gieson. The others vary in size and are usually poor in blood. Only a few are well filled with blood. The loops of these glomeruli are much clotted by protoplasmic and hyaline masses. Frequently they show some increase in the number of nuclei (fig. 15). Most of the glomeruli are adherent to the capsules, frequently to a large extent. Typical necroses of the glomeruli have not been seen. In the glomerular spaces one finds occasionally coagulated protein. In some instances the capsules are thickened by masses stained red by Van Gieson. *The covering cells of the tufts as well as the parietal epithelial cells are frequently increased in number* (fig. 15). Typical crescents are not seen.

The parenchyma of the kidneys is penetrated by many large scars which are rich in collagenous connective tissue and capillaries dilated with blood. Frequently they contain round cell infiltrations. The tubules of these regions are in all stages of atrophy and degeneration. Between the scars relatively few islands of better preserved tubules are seen which are dilated and filled with coagulated protein, hyaline droplets, some desquamated epithelial cells and some polymorphonuclear leucocytes. Some of their epithelial cells are flattened. Others are swollen. Occasionally one sees signs of regeneration. Many hyaline casts are seen within the tubules.

The arterioli show a high degree of endarteritis and occasionally hyalinization of their walls. The larger arteries show an advanced intimal hyperplasia which frequently has led to occlusion of the arteries. They are very rich in elastic and collagenous fibres. The tubules of the medulla are partly degenerated and are filled with a similar exudate to that of the cortex.

Anatomical diagnosis. Secondary contracted kidneys. Chronic glomerulonephritis. Secondary arteriosclerosis.

Case 40. Hospital No. 5119. R. S., female, 31 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

Seven years before admission the patient had diphtheria. A few months later edema appeared and albumin and casts were found in the urine. During the next 4 years she had intermittent edema, which reappeared after a severe cold 6 months before admission. The last two months nausea and vomiting were present.

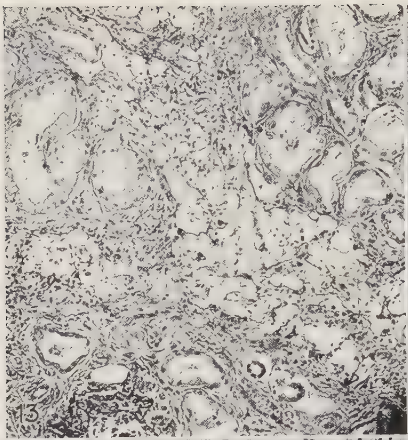
On admission gingivitis and pyorrhea alveolaris are found. The urine sediment contains a few erythrocytes and leucocytes and some hyaline and granular casts. The eyegrounds show papillary edema, hemorrhages, and white streaks of degeneration. The heart is enlarged. Blood urea nitrogen 188 mgm. per cent. Blood creatinine 4.9 mgm. per cent. Plasma cholesterol 375 mgm. per cent. Basal metabolic rate −21.4 per cent.

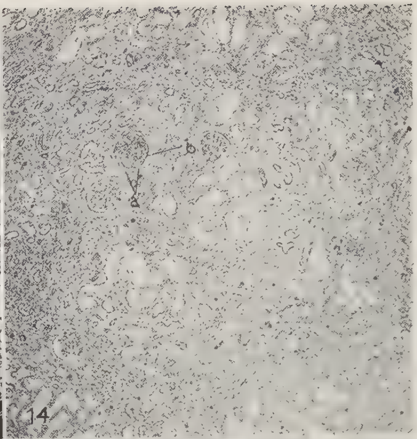
During observation the patient complained of headache and itching of the skin. The blood pressure rose to 190/120 and the blood creatinine to 9.10 mgm. per cent. Six months after admission the patient died at home with a hemiparesis. No autopsy.

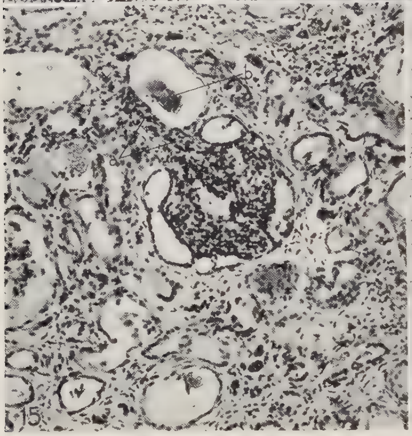
Case 41. Hospital No. 6180. M. F., female, 30 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

The patient had had severe headaches 4 years before admission. She had been told her blood pressure was 170 mm. at that time, also that there was albumin in her urine. After removal of her tonsils one year later, her blood pressure had fallen to 130 mm. One year prior to admission recurrent vomiting attacks had occurred. These attacks had become more frequent during the year. Edema had started two months before admission. At no time had there been gross hematuria or edema.

On admission to hospital there was cardiac enlargement but no signs of valvular disease. Both kidneys were palpable. The urine showed a quantity of albumin. The urinary sediment contained numerous red blood cells, no casts were seen. The blood urea N was 44 mgm. per cent, creatinine 4.5 mgm. per cent. NPN was 78 mgm. per cent, the plasma cholesterol 300 mgm. per cent. The 2 hour return of phthalein was 21 per cent of the amount intravenously injected.







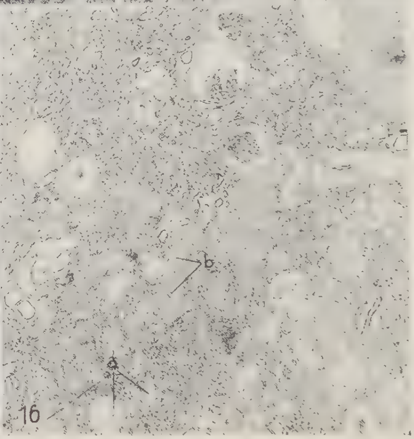


FIG. 13. Case 38. For diagnosis see figure 11.

The interstitial tissue contains a large nest of xanthoma-like lipoid cells. The tubules have undergone fatty degeneration. Mueller-formalin fixation, elastica-Van Gieson. ×200.

FIG. 14. Case 39. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

The tufts of the glomeruli are clotted and frequently adherent to the capsules (*a*). The covering cells of the tufts are increased in number (*b*). The arterioli show an endarteritis. The tubules are atrophic and degenerated in part, and contain desquamated epithelial cells, polymorphonuclear leucocytes and coagulated protein. Zenkers, iron-hematoxylin-eosin. ×60.

FIG. 15. Case 39. For diagnosis see figure 14.

The loops of the glomerulus are clotted and frequently adherent to the capsule. The endothelial cells of the glomerulus, the covering cells of the loops, and the parietal epithelial cells are increased in number. In (*a*) marked endarteritis of the afferent arteriolus. In the tubules (*b*) polymorphonuclear leucocytes and cellular detritus. Mueller-formalin fixation, iron-hematoxylin-eosin. ×200.

FIG. 16. Case 41. Anatomical diagnosis: combined chronic glomerulonephritis, arterial and arteriolar sclerosis, and pyelonephritis. Clinical diagnosis: terminal hemorrhagic nephritis, plus arteriosclerotic nephritis.

The glomerular spaces are much dilated. Many glomeruli are hyalinized (*a*). The arteries show an advanced degree of arteriosclerosis (*b*). Some of the tubules are dilated and contain casts and some cellular detritus. Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

During the 7 months that the patient was under observation, the blood urea N increased from 44 mgm. to 128 mgm. per cent, and the creatinine to 9.2 mgm. per cent. The phthalein excretion fell gradually to 5 per cent return of the dye in 2 hours. During the last 4 months the patient vomited continually and often became semi-comatose. Hemorrhages appeared in the fundi, and symptoms of increasing heart failure occurred. The patient died in uremic coma.

Autopsy. Autopsy No. 303/1928. Autopsy commenced 3 hours after death.

Uremic hemorrhages in the intestine. Cardiac hypertrophy. Small areas of bronchopneumonia. Serous pericarditis. Advanced arteriosclerosis of the spleen. Advanced atherosclerosis of the coronary arteries. Moderate atheromatosis of the aortic cusp of the mitral valve and of the aorta.

Each kidney weighed about 70 grams. The capsule stripped easily. Both kidneys were firm. The surface was coarsely granulated, showing brown red deepenings and yellowish elevations. The cortex was much narrowed and could no longer be differentiated from the medulla. The cut surface was yellowish and mottled red brown. In a few places of the medulla small abscesses were seen containing pale yellowish pus (Staphylococcus aureus, B. Proteus). The mucous membrane of pelvis and ureter of both sides was swollen and contained large hemorrhages. Also in the bladder a number of small hemorrhages were seen. Microscopically these organs showed the picture of a fresh hemorrhagic inflammation containing Gram positive cocci.

Microscopic examination. Nearly all arterioli are severely diseased (figs. 16 and 17). They are *rich in hyaline* and, in part, contain fat. Many arterioli show *endarteritis* of varying degree. In these vessels one finds occasional *necroses of the walls* as demonstrated by decay of the tissue and by the appearance of material stained bluish by Gram. In the larger arteries one sees an advanced degree of *intimal hyperplasia.*

A very large number of glomeruli are entirely hyalinized and many are stained red by Van Gieson. Others are stained yellowish. The remaining *glomeruli are very irregular in size and show tufts empty of blood and clotted with protoplasma and hyaline substances.* A few seem to be well preserved and filled with blood. Occasionally one sees *necroses* of the tufts (fig. 18). Some more severely changed glomeruli are adhesive to the capsules and contain fat. The glomerular spaces are much dilated (fig. 16). Frequently one sees coagulated protein in these spaces. In many instances, the capsules are thickened by masses stained red by Van Gieson.

The parenchyma of the kidneys is penetrated by diffuse scars which are rich in collagenous connective tissue and capillaries dilated with blood. Frequently they contain round cell infiltrations and occasionally calcium. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. Their lumina are filled with hyaline casts. The tubules of the better preserved regions are extremely dilated and contain coagulated protein, casts, some desquamated epithelial cells, and, in some places, also hemorrhages and polymorphonuclear leucocytes. The epithelial cells are flattened and some contain fat.

The medulla contains some large areas the centers of which are necrotic and filled mainly with polymorphonuclear leucocytes which are often degenerated (fig. 19). These areas are surrounded by young granulation tissue. The surrounding tissue is much changed. Its tubules are degenerated and filled by many polymorphonuclear leucocytes. The interstitial tissue, here, is edematous and infiltrated by many polymorphonuclear leucocytes. Frequently one finds hemorrhages.

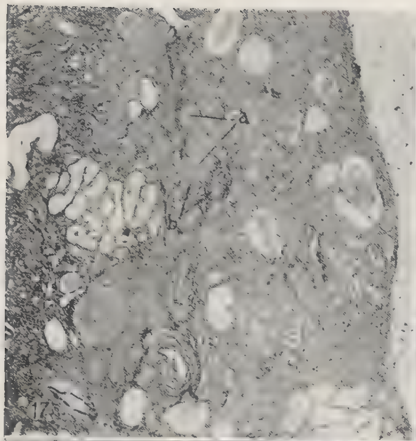
Anatomical diagnosis. Combined primary and secondary contraction kidneys. Arterio- and arteriolosclerosis. Chronic glomerulonephritis. Fresh hemorrhagic purulent pyelonephritis (Staphylococcus aureus, B. Proteus).

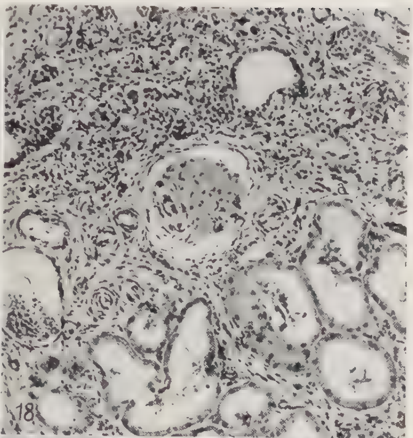
Case 42. Hospital No. 5755. F. F., male, 31 years. *Hemorrhagic Bright's disease.* Terminal, following latent → exitus.

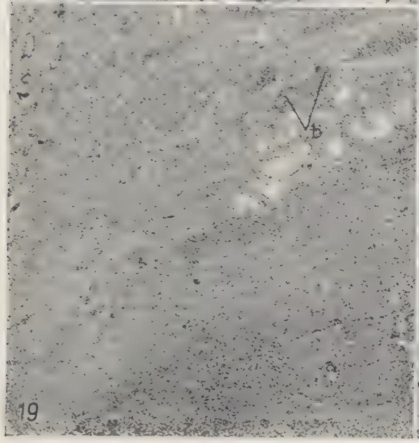
The patient had had gross hematuria, not accompanied by edema, 3 years prior to admission. He had been told that he had Bright's disease at that time. He had had no known infection previously. Hematuria soon subsided and he had felt quite well. Apparently the disease became latent for about 2 years. Eight months before admission, however, his feet became swollen. Four months later daily vomiting attacks had occurred. One month before admission he had become very dyspneic.

On admission the patient was in uremia. There was pitting edema of lower extremities. The blood pressure was 198 mm. systolic, and 104 mm. diastolic. The blood urea N was 175 mgm. per cent, the creatinine 15 mgm. per cent, and the hemoglobin 6.7 volumes per cent O_2 capacity. A 12 hour concentrated specimen of urine revealed an excretion of 1.0 gram of protein, 1,500,000 red blood cells, 800,000 white blood cells and epithelial cells, and 54,240 casts, all of which were of the Addis failure type.

The patient was under observation but 4 days before death. During that time the blood urea N increased to 187 mgm. per cent, and the creatinine to 16.6 mgm. per cent. The patient's death was hastened by bronchopneumonia.







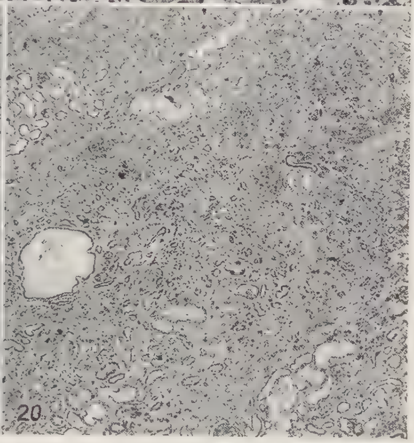


FIG. 17. Case 41. For diagnosis see figure 16.

Nearly all glomeruli (*a*) and arterioli (*b*) are hyalinized. The larger arteries show an advanced intimal hyperplasia. The parenchyma is penetrated by diffuse scars. The remaining tubules are dilated and contain hyaline casts. Mueller-formalin fixation, elastica-Van Gieson. ×60.

FIG. 18. Case 41. For diagnosis see figure 16.

Necrosis of a whole glomerulus. Endarteritis of the afferent arteriolus (*a*). The surrounding tissue is infiltrated with round cells. Mueller-formalin fixation, iron-hematoxylin-eosin. ×200.

FIG. 19. Case 41. For diagnosis see figure 16.

Purulent necrotic area (*a*) in the medulla. The surrounding tissue contains polymorphonuclear leucocytes, round cells and young fibroblasts. The tubules are filled with polymorphonuclear leucocytes (*b*). Zenkers, methylene-blue-eosin. ×200.

FIG. 20. Case 42. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

The loops of the glomeruli are almost entirely clotted and adherent to the capsules to a great extent. The capsules are thickened in most instances. Some glomeruli are entirely hyalinized. The parenchyma is penetrated by diffuse scars the tubules of which are in all stages of atrophy and degeneration. Zenkers, iron-hematoxylin-eosin. ×60.

Autopsy. Autopsy No. 268/1926. Autopsy commenced 14 hours after death.

Cardiac hypertrophy. Confluent bronchopneumonia. Serofibrinous adherent pleurisy. Serofibrinous pericarditis. Ascites.

The right kidney weighed 110, the left 150 grams. The capsule stripped with difficulty. Both kidneys were doughy in consistency. The surface was slightly granulated and mottled yellowish red. Blood dots were not noted. The cortex was similar in color to the surface and well marked off from the medulla.

Microscopic examination. All glomeruli are severely diseased (fig. 20). Their tufts are almost entirely clotted and are adherent to the capsules to an extreme extent (fig. 21). Single loops can be recognized only with difficulty. Some of the glomeruli are empty of blood and consist of protoplasmic and hyaline masses. Others are necrotic and show hemorrhages in the glomerular spaces. In most instances these spaces are missing. In a few places one sees typical crescents (fig. 21). Most of the capsules are concentrically thickened and part are rich in nuclei. Many glomeruli are entirely hyalinized (fig. 20).

The parenchyma of the kidneys is penetrated by diffuse scars which are rich in collagenous connective tissue and capillaries dilated with blood. Frequently they contain round cell infiltrations. The tubules of these regions are in all stages of atrophy and degeneration. Between these scars some islands of better preserved tubules are seen which are dilated and filled with coagulated protein, polymorphonuclear leucocytes and some desquamated epithelial cells and casts (source of Addis' "renal failure casts"). Their epithelial cells are frequently flattened.

The arterioli show varying degrees of endarteritis. A few are hyalinized. The larger arteries show a moderate degree of intimal hyperplasia.

Anatomical diagnosis. Secondary contracted kidneys. Chronic glomerulonephritis.

Case 43. Hospital No. 4845. A. B., male, 7 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

About 2½ years before admission the patient had repeated tonsillitis, and albuminuria was found. This disappeared after tonsillectomy (2 years before admission), but soon reappeared and had persisted since. About 15 months before admission edema was present for 2 or 3 weeks. Three months before admission he had a period of vomiting.

On admission the urine sediment contained a few erythrocytes, leucocytes and granular casts. The eyegrounds were normal. The heart was not enlarged. Wassermann reaction negative. Blood urea nitrogen 196 mgm. per cent. Blood creatinine 5.08 mgm. per cent.

Uremia was present throughout observation. The systolic blood pressure remained about 100 mm. The diastolic gradually fell to 40. The blood urea nitrogen rose to 692 mgm. per cent and creatinine to 16.5 mgm. per cent. Death occurred in uremia. No autopsy.

Case 44. Hospital No. 4661. M. F., female, 25 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

Between 5 and 1½ years before admission the patient had 3 attacks of peri-tonsillar abscess. After the last attack tonsillectomy was performed. Two months before admission edema gradually appeared.

On admission the urine sediment contained many erythrocytes and leucocytes, some hyaline, granular, and cellular casts, and a few erythrocyte casts. The eyegrounds showed papillary edema and exudates and a few hemorrhages. The blood pressure was 180/120. The heart enlarged. Wassermann reaction negative. Blood urea nitrogen 87 mgm. per cent.

During the first month of observation the blood pressure fell to 155/100 and remained at this level for 6 months. Fourteen months after admission it was 115/80. At this time the retinitis had also practically disappeared. Blood urea nitrogen rose slowly, however, and was 208 mgm. per cent 14 months after admission.

The patient died at home 25 months after admission.

Case 45. Hospital No. 6498. L. K., male, 39 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

The patient had had a nephrectomy (right) 6 years before admission for renal calculus. Gross hematuria had occurred 4 years later, clearing up spontaneously. Hematuria again occurred the following year, lasting a few days. The left kidney pelvis had been irrigated frequently for a year preceding admission. Six weeks before admission headaches started. These were accompanied by blurring of vision and attacks of vomiting.

On admission the patient was in uremia. The blood pressure measured 165 mm. systolic, and 115 mm. diastolic. The blood urea N was 108 mgm. per cent, and the NPN of the plasma was 138 mgm. per cent. The urine sediment contained large numbers of red blood cells and broad Addis failure casts. The protein excretion in the urine was heavy. Only a faint trace of phenolsulphonephthalein was returned in 2 hours.

During the month that the patient was under observation, the blood urea N rose to 178 mgm. per cent. The blood pressure remained elevated. The day preceding death the blood creatinine was 26.4 mg. per cent.

Autopsy. Autopsy No. 305/1928. Autopsy commenced 1 hour after death.

Death in uremia. Cardiac hypertrophy. Serous fibrinous pericarditis. Chronic cholelithiasis. Advanced atherosclerosis of the aorta.

The right kidney was missing, also the right ureter (nephrectomy). The left kidney weighed 125 grams. Its capsule stripped with difficulty. The surface was finely and coarsely granulated. Blood dots were not noted. On section the kidney showed a dilated pelvis with very little parenchyma remaining. Cortex and medulla could not be differentiated. They were grayish brown in color. The left ureter was dilated from the pelvis to the ureteral opening in the bladder.

Microscopic examination. All glomeruli are more or less diseased. Some are very large and rich in nuclei. Others are hyalinized. Their capillary loops are frequently clotted and empty of blood (fig. 22). Some contain many polymorphonuclear leucocytes. Occasionally one sees necroses and fibrin in the tufts. Most of the glomeruli are adherent to the capsules. *The covering cells of the tufts are frequently increased in number and desquamated* (fig. 22). The capsules are concentrically thickened in places by masses stained red by Van Gieson.

The parenchyma is penetrated by many scars which are rich in collagenous connective tissue and capillaries dilated with blood. Frequently one sees round cell infiltrations. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. Between the scars one sees islands of better preserved tubules, most of which are dilated and filled with coagulated protein, casts, relatively many desquamated epithelial cells, and some polymorphonuclear leucocytes. Their epithelial cells are swollen and degenerated. Hyaline-droplet degeneration is distinct in a few places. Occasionally one sees signs of regeneration.

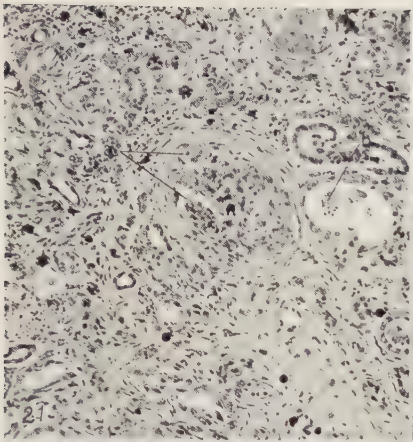
The arterioli show a moderate endarteritis and, in some places a slight hyalinization. The larger arteries are in an advanced stage of intimal hyperplasia. The tubules of the medulla are dilated and filled with a similar exudate to that of the cortex.

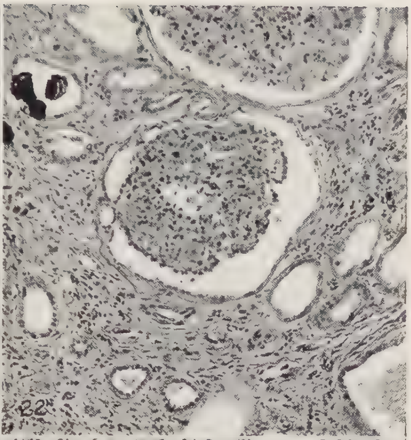
Anatomical diagnosis. Secondary contracted kidney. Chronic glomerulo-nephritis. Hydronephrosis. Secondary arteriosclerosis.

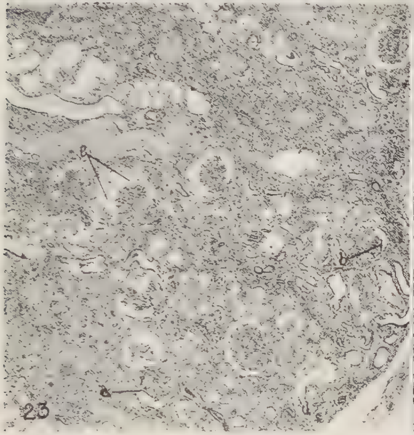
Case 46. Hospital No. 5388. B. G., male, 24 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

Seven months before admission the patient had sore throat and bronchitis. This was followed by edema and hematuria.

On admission chronic tonsillitis and pyorrhea alveolaris were found.







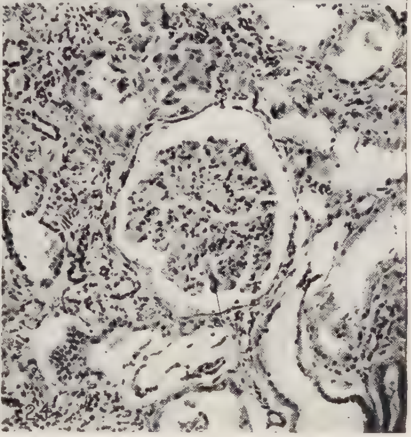


FIG. 21. Case 42. For diagnosis see figure 20.

The loops of the glomerulus are entirely clotted with protoplasmic and hyalin masses and are adherent to the capsule. The capsule is thickened. In (*a*) a crescent formation. In the tubule (*b*) one sees some polymorphonuclear leucocytes. Zenkers, iron-hematoxylin-eosin. ×200.

FIG. 22. Case 45. Anatomical diagnosis: chronic glomerulonephritis. Clinical diagnosis: terminal hemorrhagic nephritis.

The glomerulus is enlarged and rich in endothelial cells and polymorphonuclear leucocytes. The loops are clotted with hyaline and protoplasmic masses and are adherent to the capsule. The covering cells of the tufts and the parietal epithelial cells are increased in number. Zenkers, iron-hematoxylin-eosin. ×200.

FIG. 23. Case 47. Anatomical diagnosis: combined chronic glomerulonephritis and arterio- and arteriolar sclerosis. Clinical diagnosis: nephritis, terminal hemorrhagic and arteriosclerotic.

The tufts of all glomeruli are clotted with hyaline and protoplasmic masses. Some glomeruli are enlarged and adherent to the capsules (*a*). The covering cells of the tufts and the parietal epithelial cells are frequently increased in number (*b*). The capsular spaces are dilated and filled with coagulated protein and some desquamated cells (*c*). Many glomeruli are entirely hyalinized. The parenchyma is penetrated by scars which contain tubules in all stages of degeneration and atrophy. Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

FIG. 24. Case 47. For diagnosis see figure 23.

The glomerulus is enlarged and contains somewhat increased numbers of endothelial cells. The loops are clotted with protoplasmic and hyaline masses. In (*a*) one sees a necrosis of a loop. Mueller-formalin fixation, iron-hematoxylin-eosin. ×200.

There was a left dry pleurisy and some dullness over the left apex. No râles. The urine sediment contained some erythrocytes, leucocytes and hyaline and granular casts. The eyegrounds were normal. The blood pressure was about 120/80, the heart somewhat increased. Wassermann reaction negative. Blood urea nitrogen 108 mgm. per cent. Blood creatinine 5.77 mgm. per cent. Basal metabolic rate −18.7 per cent.

Between 3 and 12 months after admission the blood pressure rose to 146/90, blood urea nitrogen to 462 mgm. per cent and blood creatinine to 30.0 mgm. per cent. Death occurred in uremia.

This case is of especial interest because it ran its entire observed course with practically normal blood pressure.

Case 47. Hospital No. 6523. E. F., male, 54 years. *Hemorrhagic Bright's disease.* Terminal + arteriosclerosis → exitus.

The patient had been told 3 years before admission that his blood pressure was high. Six months before admission he had had a collapse while working. His systolic blood pressure level at that time had been 300 mm. Dyspnea had continued to become aggravated for six months prior to his admission.

Peripheral arteries were thickened and tortuous. The blood pressure was 190/130. There was cardiac enlargement and moderate edema. The blood urea N was 45 mgm. per cent, the non-protein nitrogen 70 mgm. per cent, and the hemoglobin 17 volumes per cent O_2 capacity. The phthalein excretion was 16 per cent in 2 hours. The plasma cholesterol was 195 mgm. per cent. A concentrated specimen of urine revealed an excretion of 74,000,000 red blood cells, 3,000,000 white blood cells, and epithelial cells, and 970,000 casts in 12 hours. Of the casts, 12 per cent were of Addis' failure type. The protein excretion in the urine was 10 grams per day. The plasma proteins were normal.

During the subsequent nine months that the patient was under observation, the blood pressure remained elevated, the blood urea N varied between 45 mgm. per cent and 200 mgm. per cent. The phthalein excretion decreased to a trace in 2 hours. The protein excretion in the urine decreased from 10 grams per day to 2 grams per day, but red blood cells and casts continued to be excreted in large numbers. Signs of increasing heart failure were present during the last five months; fluid accumulated to such an extent that it was necessary to perform a paracentesis. Throughout the last month of the patient's illness, extreme emaciation occurred. The blood urea N was 200 mgm. per cent during the last week of his illness. Death occurred after several hours in coma.

Autopsy. Autopsy No. 323/1929. Autopsy commenced 11 hours after death.

Death by cardiac and renal insufficiency. Cardiac enlargement. Ascites. Old adhesive pericarditis and pleurisy. Old healed endocarditis. Cholelithiasis. Advanced arteriosclerosis of the spleen. Advanced atherosclerosis of the aortic cusp of the mitral valve, of the coronary arteries and of the aorta.

The right kidney weighed 55, the left 65 grams. Both kidneys were firm. The capsules stripped with difficulty. The surface was finely and coarsely granulated and yellowish gray in color on a red brown background. In a few places blood dots were seen. The cortex was much narrowed and similar in color to the surface. Cortex and medulla could not well be differentiated.

Microscopic examination. Nearly all glomeruli are more or less changed and vary in size (fig. 23). A few are well filled with blood. Most of them are empty. *Their tufts are clotted with protoplasmic and hyaline masses in most instances* (fig. 24). Their nuclei appear to be increased in number. Frequently one sees partial necroses of the tufts (fig. 24). The afferent arterioli are often dilated with blood. The glomeruli are adherent to the capsules in many places. Especially in these glomeruli one sees a marked increase in the number of the covering cells of the tufts. In some places one finds typical crescents. The capsular spaces are frequently dilated and contain coagulated protein, and desquamated epithelial cells. The capsules are often thickened. Many glomeruli are entirely hyalinized and stained yellowish or red by Van Gieson. The more severely changed glomeruli contain much fat, but no lipoids.

The arteries and arterioli are severely diseased (fig. 25). The medial layer in the larger arteries is much thickened. Their intimal layer is in an advanced stage of intimal hyperplasia. *The walls of the arterioli are frequently thickened and hyalinized.* They are rich in fat in many instances. In some places they show endarteritis. Many smaller arteries are entirely closed.

The parenchyma of the kidneys is penetrated by many scars which are rich in collagenous connective tissue and capillaries dilated with blood. They contain round cell infiltrations. The tubules of these regions are in all stages of atrophy and degeneration up to entire disappearance. Between the scars islands of better preserved tubules are seen some of which are dilated. Their epithelial cells are mostly flattened. The tubules of the cortex contain numerous casts, and in some places coagulated protein, cellular detritus and desquamated epithelial cells. At one place in the cortex one sees a well limited trabecular cystoma (papillary adenoma) the epithelial cells of which are equal in size and do not show karyokinetic figures. The interstitial tissue of the medulla is scarred in some places.

Anatomical diagnosis. Combined primary and secondary contracted kidneys. Chronic glomerulonephritis. Arterio- and arteriolosclerosis. Papillary adenoma.

Case 48. Hospital No. 6166. D. B., female (colored), 33 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

From 6 to 3 months before admission edema of the feet was present. It reappeared one month before admission.

On admission the urine sediment contained many erythrocytes, some leucocytes, many granular and erythrocyte casts, but no doubly refractive bodies. Chronic tonsillitis was present. The eyegrounds were normal. The heart was somewhat enlarged. Wassermann reaction was negative. Blood urea nitrogen 103 mgm. per cent. Blood creatinine 7.31 mgm. per cent. Plasma cholesterol 344 mgm. per cent. Basal metabolic rate +0.3 per cent.

During observation the urine sediment did not change much except for a decrease in the number of erythrocytes. The tonsils and adenoids were removed 3 months after admission, and the patient was discharged without significant change in her outlook. Two months later she returned, with signs of cardiac failure. The standard blood urea clearance had fallen to 5 per cent of normal—about half its former value. Vomiting and twitching developed, and failure of vision, the result of an albuminuric retinitis. Death in uremia occurred 3 weeks after the second admission. Autopsy was refused.

Case 49. Hospital No. 5760. H. G., male, 47 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

Six months before admission the patient for a time had frequent vomiting. The last 3 months before admission headaches were present. Five weeks before admission hypertension was found.

After admission vomiting was frequent. The urine sediment contained many erythrocytes, some leucocytes and many broad granular casts. The eyegrounds were normal. The heart was somewhat enlarged. Blood urea nitrogen 306 mgm. per cent and blood creatinine 13.04 mgm. per cent.

During treatment with intravenous salt and glucose infusions the uremic symptoms soon disappeared, the blood urea nitrogen fell to about 85 mgm. per cent and the blood creatinine to about 5 mgm. per cent. The blood pressure increased. When last seen 3½ months after admission the blood pressure had risen to about 220/115. The patient died at home in uremia. No autopsy.

Case 50. Hospital No. 5820. F. M., male, 27 years. *Hemorrhagic Bright's disease.* Terminal → exitus.

For the last 2 years before admission the patient had chronic tonsillitis. Five months before admission he caught a cold, with severe cough. During the next month paleness, dyspnea, tiredness and headaches appeared. Tonsillectomy was then performed. Two months before admission eye ground changes, proteinuria, hematuria and hypertension were found.

On admission the patient was drowsy and complained of itching and nausea. He vomited frequently, and there were occasional nose bleeds. The urine sediment contained some erythrocytes, a few leucocytes and many hyaline and granular casts. The left eyeground shows hemorrhage and white exudative spots. The heart was somewhat enlarged. Blood urea nitrogen 308 mgm. per cent. Blood creatinine 17.65 mgm. per cent. Plasma cholesterol 227 mgm. per cent.

During the 6 weeks until death the signs of uremia increased further. The blood urea nitrogen rose to a maximum of 416 mgm. per cent, the creatinine to 25.8 mgm. per cent. The blood pressure oscillated about 160/105.

ARTERIOSCLEROTIC BRIGHT'S DISEASE (ADDIS) OR NEPHROSCLEROSIS (VOLHARD AND FAHR)

GENERAL COURSE OF THE DISEASE

The most striking clinical features are the increase in blood pressure, and the cardiac hypertrophy, plus slight proteinuria.

As pointed out by Volhard and Fahr (1914) there are two types of the disease, the benign and the malignant.

In both forms the first clinical sign is hypertension, and the first pathological changes appear to be in the small arteries.

In the benign form the nature of the disease continues unaltered to the end, which usually does not come until many years after the first appearance of hypertension. The symptoms are almost entirely those attributable to the circulatory changes, and death eventually comes usually from circulatory rather than renal failure.

In the malignant form a rapid decrease in renal function adds itself sooner or later to the picture, and death follows, usually within some months, with symptoms of renal failure, to which are frequently added those of cardiac failure. Volhard and Fahr (1914) attributed the severe nature of these cases to the superposition of glomerular inflammation upon arteriolar disease and call it the "Kombinationsform." They consider that the end of the benign stage is marked by the development of retinitis.

The material representing arteriosclerotic disease in our series (cases 51 to 56) is scanty, particularly in relation to the incidence of this condition, which is believed to occur more frequently than other forms of renal disease. Furthermore our six cases would give one the erroneous idea that renal failure is regular in this type of disease. The reason for both these discrepancies, between our cases and the ones ordinarily met showing hypertension plus slight albuminuria, is that during the period when our observations were gathered only patients with definite renal disease were admitted to the clinic. This policy excluded the great majority of arteriosclerotic cases, because their renal signs are slight until they approach the terminal stage or the malignant development sets in.

Nevertheless these cases illustrate definite features of the disease.

Case 53 shows the transition from a benign to a malignant nephrosclerotic case. The patient was admitted with no clinical signs of renal failure, normal blood creatinine, and normal eyegrounds. Fifty per cent of injected phthalein was excreted in two hours. Only the blood urea clearance, 50 per cent of normal, indicated some decrease in renal ability. The clinical symptoms were purely those of hypertension, which had been present for eight years. Six weeks after admission protein excretion, previously only 0.3 to 0.5 gram per 23 hours, increased to 4 to 5 grams, and a rapid decrease in blood urea clearance and hemoglobin content set in. Within a month renal function had sunk to practically zero, and death occurred with symptoms combining those of uremia and cardiac failure (autopsy findings below). Cases 54 and 55 also are of the malignant type.

However, the other three cases indicate that diminished renal function can also occur ultimately in the benign, slowly progressing forms of the disease. Nos. 51, 52 and 53 showed the clinical characteristics of the benign type, and no. 51 at autopsy also showed the anatomical characteristics. Yet all three showed marked loss of renal function, and two of them, nos. 51 and 56, died in the hospital with gross nitrogen retention and the clinical symptoms of uremia, added in no. 51 to those of cardiac failure.

For explanation of the following charts see p. 282, preceding the charts of the hemorrhagic cases.

CLINICAL OBSERVATIONS IN CASES OF ARTERIOSCLEROTIC BRIGHT'S DISEASE (CASES 51 TO 56)

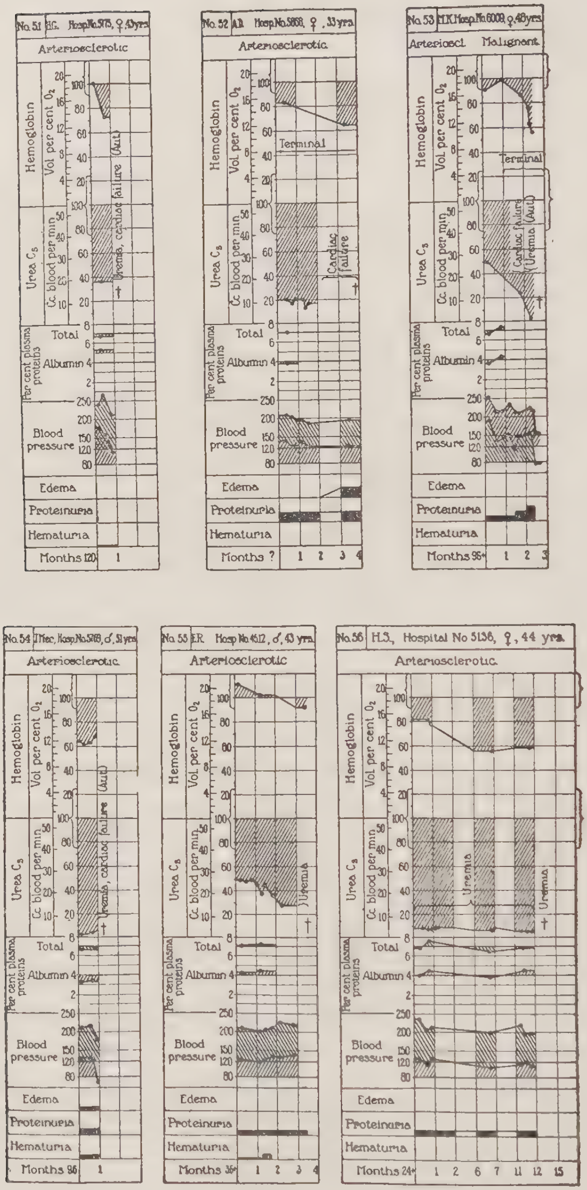
Blood urea clearance. This is low in all cases, a fact which must not be accepted as typical of any except the terminal stage of the disease, in which all of these patients were. Cases 51 and 55 died with symptoms of uremia, which, as we have stated before, are usually associated with blood urea clearances below 5 per cent of normal. Although the charts do not show it, it is practically certain that at the onset of uremia the clearances were down to this level. They were not determined, but the blood urea nitrogen values, 162, and 181 mgm. per 100 cc., were such as always accompany such clearances. In cases 53, 54 and 55, clearances in the neighborhood of 5 per cent were found, which are usual in renal deaths. It may be concluded that renal failure in all these 5 cases either was the immediate cause of death, or was sufficiently severe to have produced death in a short time, without the assistance of cardiac failure. The latter was obviously present in 4 of the 6 cases presented.

Hematuria. A microscopic hematuria is present in 3 of the 6 cases. This presumably is a terminal phenomenon. Volhard and Fahr (1914) report microscopic hematuria as rare, and Addis (1925, 1928) uses the lack of it to differentiate between the hemorrhagic and arteriosclerotic types of Bright's disease.

Blood pressure. Hypertensions, systolic as high as 200 to 250 mm., and diastolic over 120 mm., are shown by all of our cases. Again we must recall that these are terminal cases, that during most of the long course of the disease the blood pressures were undoubtedly lower, and reached their terminal heights only through increase during periods of years. Volhard and Fahr (1914) report cases with relatively moderate hypertensions, such as 170 systolic.

Plasma protein content. In all of these cases the plasma protein contents were entirely normal.

Proteinuria was present in all cases, but exceeded 1 gram per day in


No. 51 H.G. Hosp. No. 5175, ♀, 43 yrs.
Arteriosclerotic
No. 52 A.B. Hosp. No. 5868, ♀, 33 yrs.
Arteriosclerotic
No. 53 M.K. Hosp. No. 6009, ♀, 48 yrs.
Arteriosc1. Malignant
No. 54 J. Mec, Hosp. No. 5769, ♂, 51 yrs.
Arteriosclerotic
No. 55 E.R. Hosp. No. 4612, ♂, 43 yrs.
Arteriosclerotic
No. 56 H.S., Hospital No 5136, ♀, 44 yrs.
Arteriosclerotic
Hemoglobin
Vol per cent O₂
Urea C₈
Cc blood per min
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Terminal
Uremia, cardiac failure (Aut)
Cardiac failure
Cardiac failure (Uremia (Aut)
Uremia
†
Months 120 1
Months ? 1 2 3 4
Months 96+ 1 2 3
Months 96 1
Months 36+ 1 2 3 4
Months 24+ 1 2 6 7 11 12 15

CHARTS 51–56

only two of the six. In case 53 there was a marked increase (from 0.2 to 0.5 gram per day to 4 to 5 grams) with the onset of terminal malignant symptoms. In case 52 the excretion was from 1 to 3 grams per 24 hours.

Edema was present in two cases, nos. 54, and 52. It was obviously of cardiac origin.

Anemia was present in five of the six cases, but to a less extensive degree than in the terminal cases of hemorrhagic nephritis. In none of the sclerotic cases did the oxygen capacity fall below 10 volumes per cent. In case 54 a rapid fall occurred from 18 volumes per cent to 10 during the terminal six weeks of the disease, when it suddenly changed from benign to malignant.

ANATOMICAL CHANGES OBSERVED IN TERMINAL NEPHROSCLEROSIS (CASES 51, 53 AND 54)

In arterio- and arteriolosclerosis we distinguish two forms which are recognized by nearly all investigators. In the one form pure arteriosclerotic lesions are outstanding, that is to say intimal hyperplasia of the larger and medium sized arteries and hyalinization and fatty degeneration of the arterioli. In the other form besides these lesions inflammatory changes are found, such as necroses and proliferations of the arterioli and glomeruli. The first form is called by Fahr (1925) benign sclerosis and coincides with the senile arteriosclerotic kidneys of Ziegler. The second form Fahr calls malignant sclerosis; it corresponds to the genuine contracted kidneys of the literature. Whereas, perhaps, most writers, like Aschoff (1921), believe that the benign and malignant forms are only two stages of one and the same disease, Fahr (1925) believes that we have to deal with two diseases. According to Fahr the benign sclerosis is primarily a pure arteriosclerotic lesion, whereas in the malignant sclerosis endarteritis and necroses are outstanding right from the beginning. He supports his theory chiefly by the finding that benign sclerosis is mainly found in old age, whereas malignant sclerosis occurs between the ages of 30 and 60.

There is no doubt that our three cases were true vascular contracted kidneys. All three showed shrunken, coarsely granulated kidneys, reddish brown in color. Histologically we found extensive hyalinization of the arterioli and glomeruli, fatty degeneration of the arterioli and extensive intimal hyperplasia of the large and medium sized arteries. A large number of glomeruli were intact. Furthermore, the cases showed advanced atherosclerosis in other regions of the body and cardiac hypertrophy.

Case 51 essentially exhibited these lesions. Therefore, we classify it with the benign sclerosis of Fahr. In addition we found increase in the number of nuclei and occasional hyaline-droplet degeneration of some glomeruli, as well as slight necroses of some arterioli and glomeruli. But these changes were only slight. They are regarded by Fahr (1925) as symptoms of decompensation of the benign sclerosis. Aschoff (1921) would call this case a transition form from the second to the third or terminal stage. It should be noticed that this case died in uremia, an outcome believed to be relatively rare in benign sclerosis.

In cases 53 and 54 we found, besides the lesions described above, extended inflammatory changes like marked endarteritis, frequent necroses of the arteriolar walls and glomeruli, occasional increases in the number of nuclei, and adhesions of the glomeruli, as well as occasional increases in the number of the glomerular epithelial cells. In case 53 there were occasional hemorrhages in the capsular spaces, in case 54 a hyaline-droplet degeneration of some glomeruli. However, most of the glomeruli were intact. Consequently, both cases represent the malignant sclerosis of Fahr.

Both cases died in uremia.

CASE HISTORY ABSTRACTS AND AUTOPSY REPORTS (ARTERIOSCLEROTIC BRIGHT'S DISEASE) (CASES 51 TO 56)

Case 51. Hospital No. 5775. H. G., female, 43 years. *Arteriosclerotic Bright's disease.* Terminal → exitus.

The patient had suffered from headaches and dyspnea on exertion for 10 years before admission. Three years before admission she had had several attacks of vertigo and nausea. These had become more frequent and more severe. One year before admission she had been told that her blood pressure was 190, and six months before admission 280 mm. During that time edema had appeared; blurring of vision had also occurred.

On admission, the heart was found to be enlarged. The blood pressure was 245 mm. systolic, and 175 mm. diastolic. The ocular fundi showed arterial tortuosity, arterio-venous compression, and fresh hemorrhages.

The electrocardiogram revealed a left axis deviation. The urine sediment contained red blood cells and granular casts. The protein excretion in the urine was 2.3 grams daily. The blood urea N was 31 mgm. per cent, and the plasma NPN 47 mgm. per cent. The plasma proteins were normal. The hemoglobin was normal (18.5 volumes per cent O_2). The return of phenolsulphonephthalein in the urine in 2 hours was 43 per cent.

During the month that the patient was under observation evidence of cardiac failure appeared. The blood pressure remained elevated. The blood urea N increased to 162 mgm. per cent, and the creatinine to 9 mgm. per cent. The patient became comatose two days before death.

Autopsy. Autopsy No. 273/1926. Autopsy commenced 2 hours after death.

Death in uremia. Cardiac hypertrophy. Ulcus ventriculi. Advanced arteriosclerosis of the spleen. Advanced atherosclerosis of the coronary arteries and aorta.

The right kidney weighed 110, the left 140 grams. The capsule of each stripped easily. The surface was coarsely granulated and purplish red in color with occasional yellowish areas. Hemorrhages were not noted. The cortex was narrowed and similar in color to the surface. The differentiation between cortex and medulla was indistinct.

Microscopic examination. The arterioli and arteries of the kidneys are severely diseased. (fig. 26). The arterioli are hyalinized in most places. Many are entirely closed. The larger arteries show an advanced degree of intimal hyperplasia and contain calcium. At a few places in the arterial walls one sees *slight necroses.*

Many glomeruli are intact and well filled with blood (fig. 27). Some glomeruli are a little enlarged and even show *some increase in the number of nuclei* (fig. 27). Some glomeruli contain relatively many polymorphonuclear leucocytes in their loops. Single glomeruli show necroses and *hyaline-droplet degeneration.* The glomerular spaces are wide and mostly empty. Other glomeruli are atrophic and partially hyalinized, with concentrically thickened capsules. Occasionally one sees a slight increase in the number of the parietal epithelial cells. From these glomeruli one finds all transitions to entire hyalinization. Typical signs of glomerulonephritis are nowhere seen.

The tubules are relatively well preserved. Some are enlarged. A few show hyaline-droplet degeneration. In their lumina one finds coagulated protein and some desquamated epithelial cells. The parenchyma is penetrated by scars which are rich in collagenous connective tissue and capillaries dilated with blood. They contain round cellular infiltrations. The tubules of these regions are in all stages of atrophy up to entire disappearance.

Anatomical diagnosis. Primary contracted kidneys. Arteriolo- and arteriosclerosis. Decomposed benign sclerosis of Fahr.

Case 52. Hospital No. 5868. A. D., female, 33 years. *Arteriosclerotic Bright's disease.* Terminal → exitus.

The patient suffered from headaches for several years. Eight months before admission hypertension and albuminuria were accidently found.

On admission there was no cardiac decompensation. The urine sediment contains no erythrocytes, a few leucocytes and granular casts. The eyegrounds were normal. The blood pressure was about 200/135. The heart size was markedly increased to the left. Wassermann reaction negative. Blood urea nitrogen 48 mgm. per cent. Blood creatinine 2.73 mgm. per cent.

The blood pressure did not change during treatment. Patient died at home from suddenly developed cardiac failure 4 months after admission.

Case 53. Hospital No. 6009. M. K., female, 48 years. *Arteriosclerotic Bright's disease.* Latent → terminal → exitus.

Father died of Bright's disease with severe hypertension 8 years before the patient's admission. Hypertension (190 mm.) was accidentally found.

On admission the urine sediment contained a few erythrocytes, leucocytes and hyaline casts. The eyegrounds were normal. The blood pressure was 250/190. The heart was slightly enlarged. Blood urea nitrogen was 40 mgm. per cent. Blood creatinine was 1.78 mgm. per cent. Blood urea clearance was 50 per cent normal.

Two months after admission, the urine albumin increased from 0.5 to 3.0 gram a day. Blood urea clearance had fallen to 28 per cent of normal. Then weakness and nausea appeared, but no signs of congestive heart failure. Renal failure casts (Addis, 1925) were found in the urine. Pruritus developed, then coma, and uremic twitching. Two days before death the blood urea nitrogen was 140 mgm. per cent, and the blood creatinine 9.73 mgm. per cent. The cause of this rapid development is obscure. There may have been a cardiac factor. The syndrome is like that of malignant nephrosclerosis, the "Kombinationsform" described by Volhard and Fahr.

Autopsy. Autopsy No. 282/1927. Autopsy commenced 7 hours after death.

Cardiac hypertrophy. Fresh obliterative bronchiolitis. Serous pleurisy. Serofibrinous pericarditis. Cartilagenous perisplenitis. Old healed endocarditis of the mitral valve. Advanced arteriosclerosis of the spleen. Advanced atherosclerosis of the aortic cusp of the mitral valve, of the coronary arteries, and of the aorta.

The kidneys weighed about 75 grams each. The capsule stripped with difficulty. The kidneys were firm. The surface was brownish red and the greater part was coarsely granulated. Single blood dots were seen. The cortex was narrowed and reddish and yellowish in color. It was poorly marked off from the medulla.

Microscopic examination. Nearly all arterioli are more or less diseased (Fig. 28). Part of them are closed entirely. Most of them are hyalinized. Frequently they contain fat. Many arterioli show *endarteritis* of partly low and partly advanced degree. In these vessels one finds frequently *necroses of the wall* (fig. 29) as shown by granular degeneration of the tissue, pycnosis and karyokinesis of the nuclei, and by the appearance of substances in the wall which are stained bluish by Gram. In the larger arteries containing elastic tissue one sees advanced stages of intimal hyperplasia.

A large number of glomeruli are intact and well filled with blood. Others are atrophic. Many glomeruli show all transitions from beginning to entire hyalinization (fig. 28). One sees glomeruli the tufts of which are partly hyalinized. Such tufts appear to be attached to hyalinized arterioli. In other glomeruli such transitions cannot be found and the chief change is hyalinization of the loops. Hyalinization of the capsules is seen only with advanced stages of glomerular hyalinization. In partially hyalinized glomeruli there is frequently dilatation of the afferent arterioli. Frequently *necrosis of the tufts* occurs, usually located in a single loop and very rarely affecting an entire glomerulus (fig. 30). In such glomeruli single or all loops may be dilated with blood, and very few hemorrhages may be seen in the glomerular spaces. In severely changed glomeruli one sees occasionally adhesions or a slight increase in the number of the parietal epithelial cells. In a few places also a partial increase in the number of nuclei is found. Frequently the glomeruli contain relatively large amounts of fat which often is doubly refractive.

The parenchyma of the kidneys is penetrated by many scars which are rich in collagenous connective tissue, and occasionally contain small round cell infiltrations. The scars are rich in capillaries dilated with blood. The tubules of these parts are in all stages of atrophy and degeneration up to entire disappearance. Occasionally one finds calcium in these scars. The tubules of the better preserved parts are frequently dilated. In places they show flattened epithelial cells, hyaline casts, some desquamated epithelial cells, and in a few instances also some polymorphonuclear leucocytes. The epithelial cells occasionally contain a certain amount of fat, some of which is doubly refractive. Occasionally one finds signs of regeneration. The interstitial tissue of the medulla is enlarged in some places, and rich in collagenous connective tissue.

Anatomical diagnosis. Primary contracted kidneys. Arteriolo- and arteriosclerosis. Malignant sclerosis of Fahr.

Case 54. Hospital No. 5769. J. M., male, 51 years. *Arteriosclerotic Bright's disease.* Terminal → exitus.

The patient had had two attacks of renal colic 12 and 8 years before admission. After the first attack, he had suffered from headaches. He had been told at that time that his blood pressure was 170. During the year preceding admission he had edema of the feet. Dyspnea on exertion had occurred also during that time.

On admission to hospital symptoms of cardiac failure were present, i.e., edema, respiratory distress, and cyanosis. The heart was enlarged to the left. The blood pressure measured 192 mm. systolic and 118 mm. diastolic. An electrocardiogram showed left axis deviation. The urine contained 1.5 gram albumin per liter, many failure casts, and red blood cells. The blood urea N was 72.5 mgm. per cent, the creatinine 7.7 mgm. per cent, and the plasma NPN 82 mgm. per cent. The hemoglobin was 12.2 volumes per cent O_2 capacity. The plasma albumin was 3.15 per cent, and the globulin 3.52 per cent. A trace of phthalein was excreted in two hours.

During the month that the patient was under observation, the nitrogen retention increased, the blood urea N rising to 216 mgm. per cent, and the creatinine to 16 mgm. per cent. A concentrated specimen of urine revealed by Addis's count an excretion of 19,000,000 red blood cells, 400,000 failure casts, and 1,000,000 white and epithelial cells in 12 hours. During the nine days before death, the patient lost 12 kgm. in weight. He was comatose the last 5 days.

Autopsy. Autopsy No. 271/1926.

We were permitted to do only a partial autopsy. This was performed a few hours after death.

Each kidney weighed about 100 grams. The capsule stripped easily. The surface was coarsely granulated and brownish red in color with yellowish elevations. No blood dots were found. The cortex was narrowed and similar in color to the surface. The differentiation between cortex and medulla was indistinct.

Microscopic examination. The arterioli and arteries are severely diseased (fig. 31). Some of them are closed entirely. The arterioli are hyalinized and contain much fat. Many arterioli show *endarteritis* of varying degree (fig. 32). Frequently, one finds on these vessels *necroses of the walls* (fig. 32) as indicated by granular degeneration of the tissue, pycnosis of the nuclei and hemorrhages within the walls. The larger arteries show an advanced intimal hyperplasia and are partly calcified.

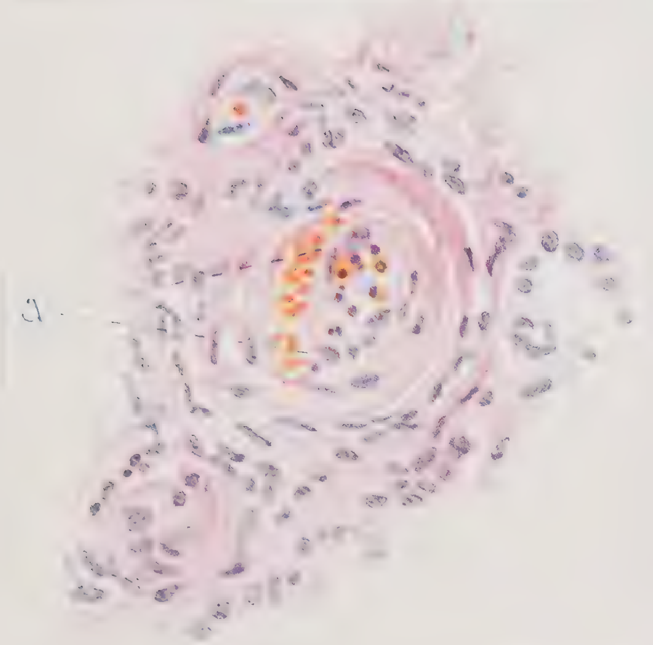
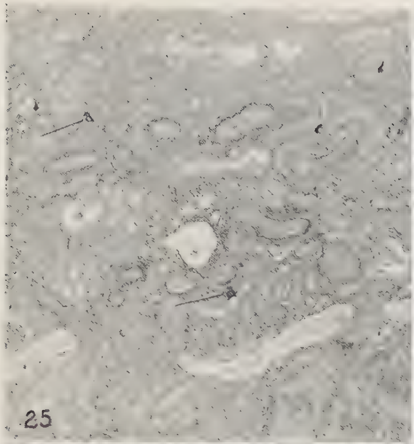
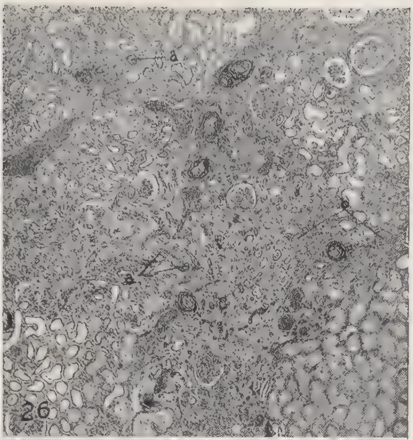
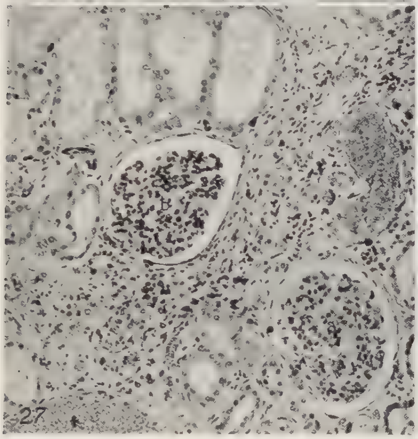


FIG. 29. Case 53. For diagnosis see figure 28.
Two arterioli with advanced endarteritis. In (*a*) necrosis of the wall with hemorrhage in the wall of the arteriole. Mueller-formalin fixation, iron-hematoxylin-eosin. ×450.







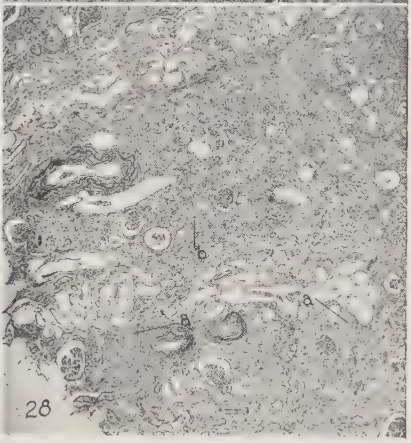


FIG. 25. Case 47. For diagnosis see figure 23.

Many glomeruli are hyalinized (*a*). The smaller and larger arteries show a high degree of intimal hyperplasia. The tubules of the scars are in all stages of atrophy and degeneration and contain many casts. Mueller-formalin fixation, elastica-Van Gieson. ×60.

FIG. 26. Case 51. Anatomical diagnosis: decomposed benign nephrosclerosis. Clinical diagnosis: arteriosclerotic Bright's disease with terminal renal and cardiac failure.

Hyalinization of the arterioli (*a*) and of some glumeruli (*b*). Advanced intimal hyperplasia of the larger arteries. Most of the glomeruli are intact. The parenchyma is penetrated by scars rich in capillaries dilated with blood (*c*). Zenkers, elastica-Van Gieson. ×60.

FIG. 27. Case 51. For diagnosis see figure 26.

(*a*) Intact glomerulus. (*b*) Glomerulus with somewhat increased numbers of endothelial cells. At the place of entrance of the arteriole beginning hyalinization. Scar formation between the glomeruli. Zenkers, iron-hematoxylin-eosin. ×200.

FIG. 28. Case 53. Anatomical diagnosis: malignant nephrosclerosis. Clinical diagnosis: arteriosclerotic Bright's disease, malignant.

Some glomeruli (*a*) and arterioli (*b*) are hyalinized. The larger arteries show an advanced intimal hyperplasia. The remaining glomeruli are intact in most instances. Mueller-formalin fixation, elastica-Van Gieson. ×60.

Many glomeruli are entirely hyalinized (fig. 31). Others show all transitions from beginning hyalinization, starting in most places in the loops, up to entire degeneration. The remaining glomeruli are intact in most places and well filled with blood. In some glomeruli one finds *necrosis of the loops, a hyaline-droplet degeneration*, some fat and a partial increase in the number of nuclei. In severely changed glomeruli one sees occasionally adhesions and a slight increase in the number of the parietal epithelial cells.

The parenchyma is penetrated by scars which are rich in collagenous connective tissue and capillaries dilated with blood. Frequently one sees round cell infiltrations. The tubules of these regions are in all stages of atrophy and degeneration. Some of the better preserved tubules are dilated and contain coagulated protein and desquamated epithelial cells. Occasionally one sees fatty degeneration of the epithelial cells. The interstitial tissue of the medulla is enlarged in places and rich in collagenous connective tissue.

Anatomical diagnosis. Primary contracted kidneys. Arterio- and arteriolosclerosis. Malignant sclerosis of Fahr.

Case 55. Hospital No. 4512. E. R. male, 43 years. *Arteriosclerotic Bright's disease.* Terminal → exitus.

Three years before admission a systolic blood pressure of 165 was accidentally found. One year later exhaustion and headaches appeared. Seven months before admission the patient was examined with the following result; blood pressure 232/135, eyes normal, some pyorrhea alveolaris, the urine contained a trace of albumin and some hyaline, granular, and waxy casts. Two-hour phthalein excretion after intramuscular injection was 37.5 per cent. Non-protein N was 30 mgm. per cent.

On admission the urine sediment contained a few erythrocytes and leucocytes and some hyaline and granular casts. The eyegrounds showed thin arteries and a few small hemorrhages. The blood pressure was about 210/125. The heart was enlarged. Wassermann reaction negative. Blood urea nitrogen 49 mgm. per cent.

During observation the blood urea nitrogen rose to 111 mgm. per cent. One month after his discharge the patient was admitted to another hospital. He was then in uremia and died a few days later. The blood urea nitrogen was then 181 mgm. per cent. No autopsy.

Case 56. Hospital No. 5136. H. S., female, 44 years. *Arteriosclerotic Bright's disease.* Terminal → exitus.

Two years before admission nocturia occurred. One year later occipital

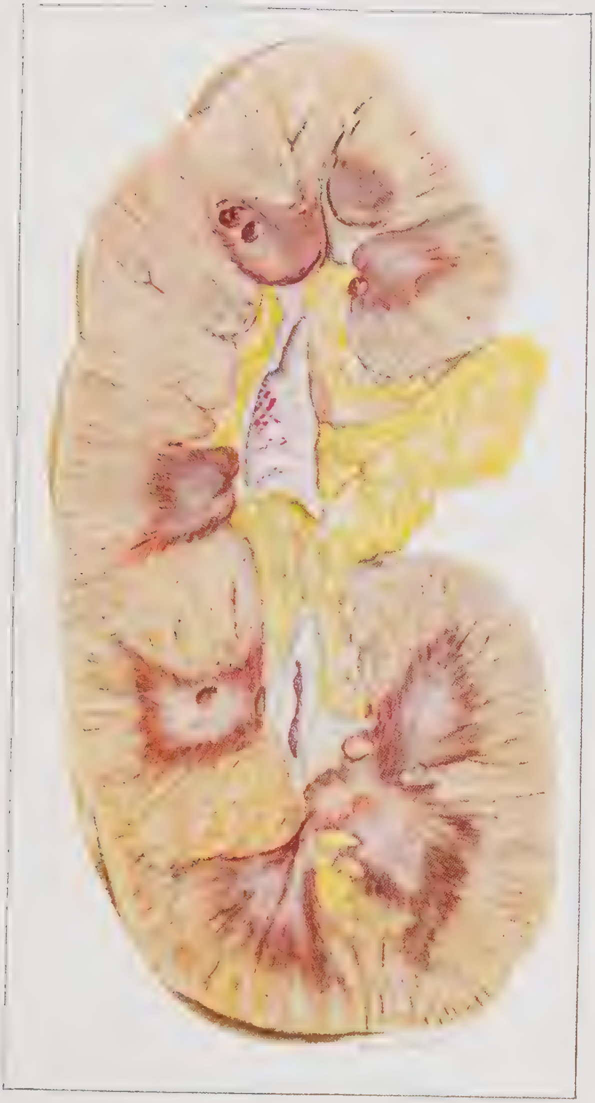
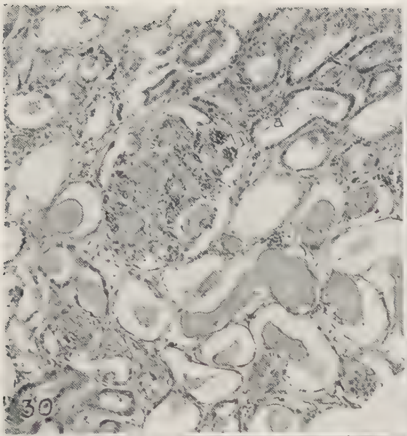
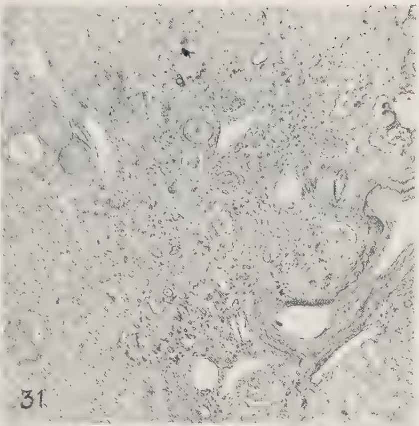
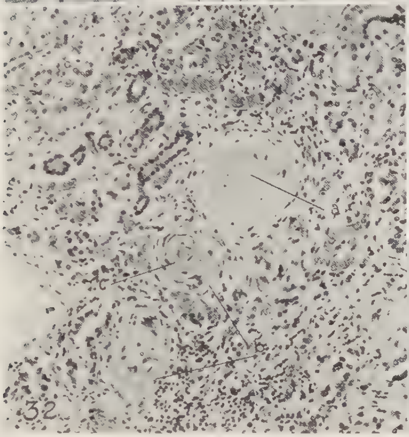


FIG. 33. Case 59. Anatomical diagnosis: lipoid nephrosis. Clinical diagnosis: chronic non-hemorrhagic degenerative Bright's disease.

Longitudinal section through the right kidney drawn after Jores fixation. Natural size.







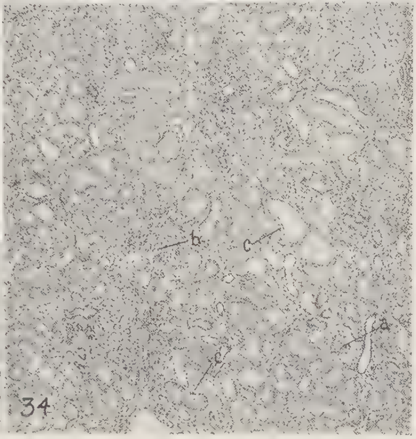


FIG. 30. Case 53. For diagnosis see figure 28.

The whole glomerulus is necrotic. Some of the loops are dilated with blood (*a*). The tubules contain many hyaline casts. Mueller-formalin fixation, iron-hematoxylin-eosin. ×200.

FIG. 31. Case 54. Anatomical diagnosis: malignant sclerosis. Clinical diagnosis: arteriosclerotic Bright's disease with terminal cardiac and renal faliure.

Hyalinization of many glomeruli. Advanced intimal hyperplasia of the smaller and larger arteries. The remaining glomeruli are intact. The parenchyma is penetrated by scars which contain capillaries dilated with blood and tubules in all stages of atrophy and degeneration. Round-cell infiltration (*a*). Mueller-formalin fixation, elastica-Van Gieson. ×60.

FIG. 32. Case 54. For diagnosis see figure 31.

(*a*) Hyalinized glomerulus. (*b*) Arterioli showing an advanced endarteritis and necrosis of their walls. (*c*) The surrounding tissue is scarred and contains a round cell infiltration. Mueller-formalin fixation, iron-hematoxylin-eosin. ×200.

FIG. 34. Case 59. For diagnosis see figure 33.

Enlarged convoluted tubules with fatty, vacuolic or hyaline-droplet degenerated epithelial cells. Distinct striped scars with infiltrations of round cells. In (*a*) one sees an intact glomerulus, in (*b*) a small intact artery, in (*c*) regeneration of epithelial cells. Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

headaches and dyspnea on exertion appeared. For the last 2 weeks before admission she had vomiting in the morning.

On admission the urine sediment contained nothing pathologic. The eyegrounds were normal. The blood pressure was 238/130 and the heart was enlarged. Blood urea nitrogen 174 mgm. per cent. Blood creatinine 8.70 mgm. per cent.

During observation the urine sediment showed only occasional leucocytes and single hyaline casts. The blood pressure was about 210/115. Blood urea nitrogen rose gradually to 297 mgm. per cent and creatinine to 11 mgm. per cent. Throughout observation she had headaches, and nausea with occasional vomiting. Fifteen months after admission, when at home, she contracted pneumonia and died in coma with convulsions. No autopsy.

Non-Hemorrhagic Degenerative Bright's Disease (Addis) or Nephrosis (Volhard and Fahr)

GENERAL COURSE OF THE DISEASE

Müller (1905) and Volhard and Fahr (1914) have pointed out the existence of a type of Bright's disease distinguished by heavy proteinuria, tendency to edema formation, usually massive, and by degenerative rather than inflammatory changes in the kidneys. The disease appears to accompany or follow a heterogeneous set of intoxications and infections, frequent among which are pregnancy, toxemia, osteomyelitis, syphilis, and tuberculosis. In many cases there is no obvious etiology: the edema begins insidiously and without previously noted illness or intoxication. Addis (1925) calls these cases "cryptic" and Volhard and Fahr term them "genuine."

The outstanding constant abnormalities in the blood are a deficit of plasma albumin, which is more often than not less than half the normal 4 per cent concentration, and an increase of the fat and cholesterol contents. The work of Starling, Epstein, Govaerts, and Schade and Claussen, and Moore and Van Slyke, quoted above in the discussion of the significance of plasma protein values, has left small room to doubt that the plasma albumin deficit is the predisposing factor for the development of edema.

The quantitative relationships between the tendency to edema formation, the deficit of albumin and total protein in the plasma, and the decrease in plasma specific gravity have been outlined in the above mentioned discussion.

The lack of 4 abnormalities that are common in hemorrhagic nephritis has been used to differentiate nephrosis from the former. These are hematuria, urea retention, hypertension, and anemia, all of which are common in chronic hemorrhagic nephritis, and may be entirely absent in nephrosis. However, of the four, *hematuria and hypertension* are the only ones we have found *uniformly absent* in our series of nephrosis cases.

With regard to nitrogen retention and ultimate uremia, data in the literature differ. Volhard and Fahr (1914) observed nitrogen retention rarely, and apparently considered it unlikely to become serious. They had not seen a death attributable primarily to renal failure. Addis on the other hand (1925) remarks: "The disease may pass through active and latent stages to complete recovery, or may gradually progress to a termination in uremia." Of our 10 cases two have progressed to final uremia with urea retention (nos. 65 and 66). Furthermore it seems safe to predict that such an outcome is probable in two others, cases 61 and 64, which for two years have shown in general a downwards tendency in their renal function, as measured by the blood urea clearance. Volhard and Fahr found part of the glomeruli altered in cases which they autopsied. It is not strange that the damage should in time proceed far enough to result in uremia. Our data indicate that the process may be slow. On the other hand, in case 66 the entire apparent duration of the disease to uremia was only a year and a half. The absence of evidence of inflammatory processes in this case was demonstrated by autopsy.

Anemia likewise is by no means uniformly absent in nephrosis. Considering the malnutrition that appears to be inherent in the disease, and the frequency with which the patients suffer from obstinate infections, the occurrence of anemia is not surprising, even when it can not be attributed to the effect of toxic retention. The effect of intercurrent infections appears to be illustrated by case 61. The hemoglobin, from a full normal value, fell after septicemia and pleurisy succeeding one another, to 40 per cent. Thereafter it gradually rose again, reaching 80 per cent within a month and ultimately 100 per cent, despite the fact the renal disease, as indicated by blood urea clearance and albuminuria, had progressed rather than improved. Of our 10 cases, only 3 in fact consistently showed hemoglobin values above 80 per cent of Haldane's average normal standard.

In the latent form of hemorrhagic nephritis, and less frequently in the chronic active stage of hemorrhagic nephritis, hematuria and hypertension, mentioned as characteristically absent in nephrosis, may be lacking, or very slight. As mentioned in discussion of these stages of hemorrhagic nephritis, differential diagnosis from nephrosis may be difficult unless there is a history of acute hemorrhagic onset. In the latent hemorrhagic disease the plasma protein deficit and albuminuria are likely to be less marked, however, than in nephrosis; and if the primarily hemorrhagic case is watched it is likely either to make a rather rapid recovery (which is not frequent in nephrosis), or else if the disease progresses to the terminal stage, to show a return of hematuria and develop a hypertension, as in case 23a.

For explanation of the following charts see page 282 preceding the charts of the hemorrhagic cases.

CLINICAL OBSERVATIONS IN CASES OF DEGENERATIVE BRIGHT'S DISEASE (CASES 57 TO 66)

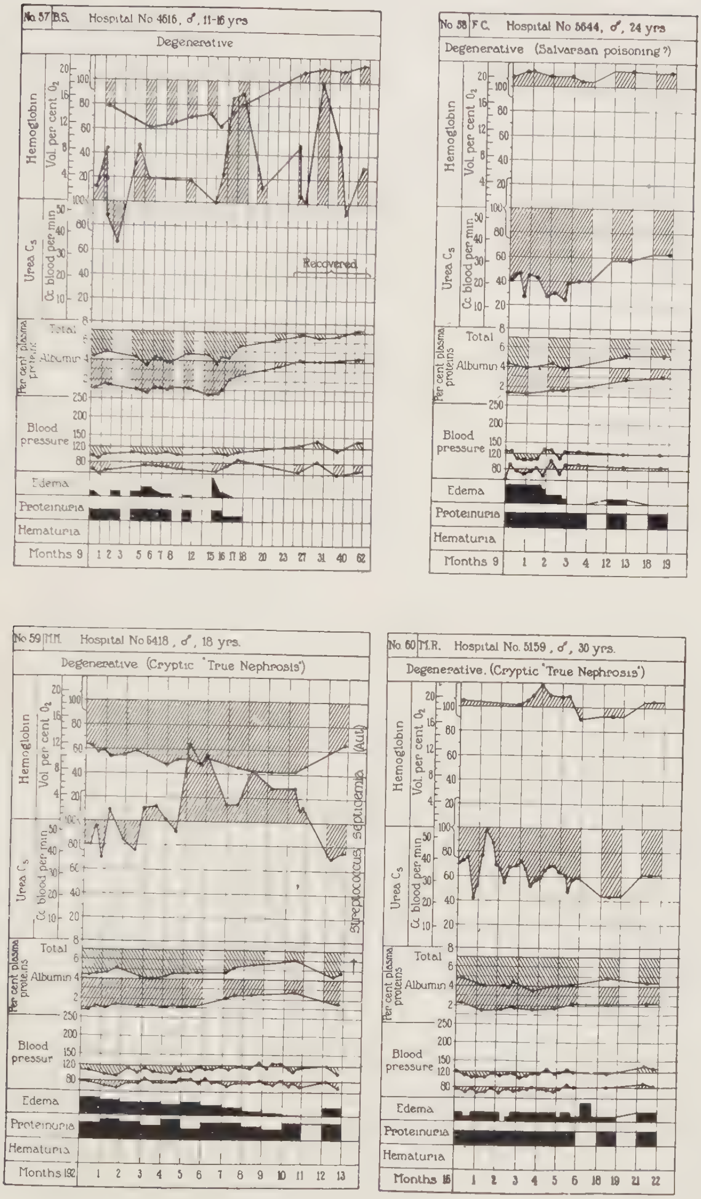
Urea excreting power. In only 2, nos. 57 and 59, of our 10 cases, was the blood urea clearance up to normal throughout the course of observation. In these two there were periods when the urea excretion was indeed hypernormal, a phenomenon elsewhere met only in cases recovering from acute hemorrhagic nephritis.

In 8 cases (nos. 58, 60, 61 and 62 to 66), there was definite fall in blood urea clearance, apparently temporary in case 58 (disease attributed to salvarsan poisoning), but showing a tendency to remain or progress in the others.

In 3 cases (nos. 63, 65 and 66) the blood urea clearance before death fell to the uremic level, and cases 65 and 66 died typical renal deaths. Case 66 at autopsy proved to be amyloid nephrosis, with extensive glomerular damage. For no. 65 autopsy was refused.

Hematuria was consistently absent in all of our cases, except for single examinations during 2 years in case 64.

Blood pressure. There was no hypertension in any case throughout the observed course of the disease. The only exception is a single observation of 154/98 on case 62 immediately after admission, which may probably be disregarded. In case 63 with tuberculosis and asthenia the pressure was abnormally low.


No 57 B.S. Hospital No 4616, ♂, 11-16 yrs
Degenerative
Hemoglobin
Vol. per cent O2
Urea Cs
Cc blood per min
Recovered
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months 9
1 2 3 5 6 7 8 12 15 16 17 18 20 23 27 31 40 62
No 58 F.C. Hospital No 5644, ♂, 24 yrs
Degenerative (Salvarsan poisoning ?)
Hemoglobin
Vol. per cent O2
Urea Cs
Cc blood per min
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months 9
1 2 3 4 12 13 18 19
No 59 M.M. Hospital No 6418, ♂, 18 yrs.
Degenerative (Cryptic "True Nephrosis")
Hemoglobin
Vol. per cent O2
Urea Cs
Cc blood per min
Streptococcus septicemia (Aut.)
Per cent plasma proteins
Total
Albumin
Blood pressur
Edema
Proteinuria
Hematuria
Months 192
1 2 3 4 5 6 7 8 9 10 11 12 13
No. 60 M.R. Hospital No. 5159, ♂, 30 yrs.
Degenerative. (Cryptic "True Nephrosis")
Hemoglobin
Vol. per cent O2
Urea Cs
Cc blood per min
Per cent plasma proteins
Total
Albumin
Blood pressure
Edema
Proteinuria
Hematuria
Months 16
1 2 3 4 5 6 18 19 21 22

CHARTS 57–60

Plasma protein concentration. Of all the chemical examinations in nephrosis that of the plasma protein concentration is of first interest, because the albumin deficit is so closely related to the tendency to edema which is the disabling factor of the disease.

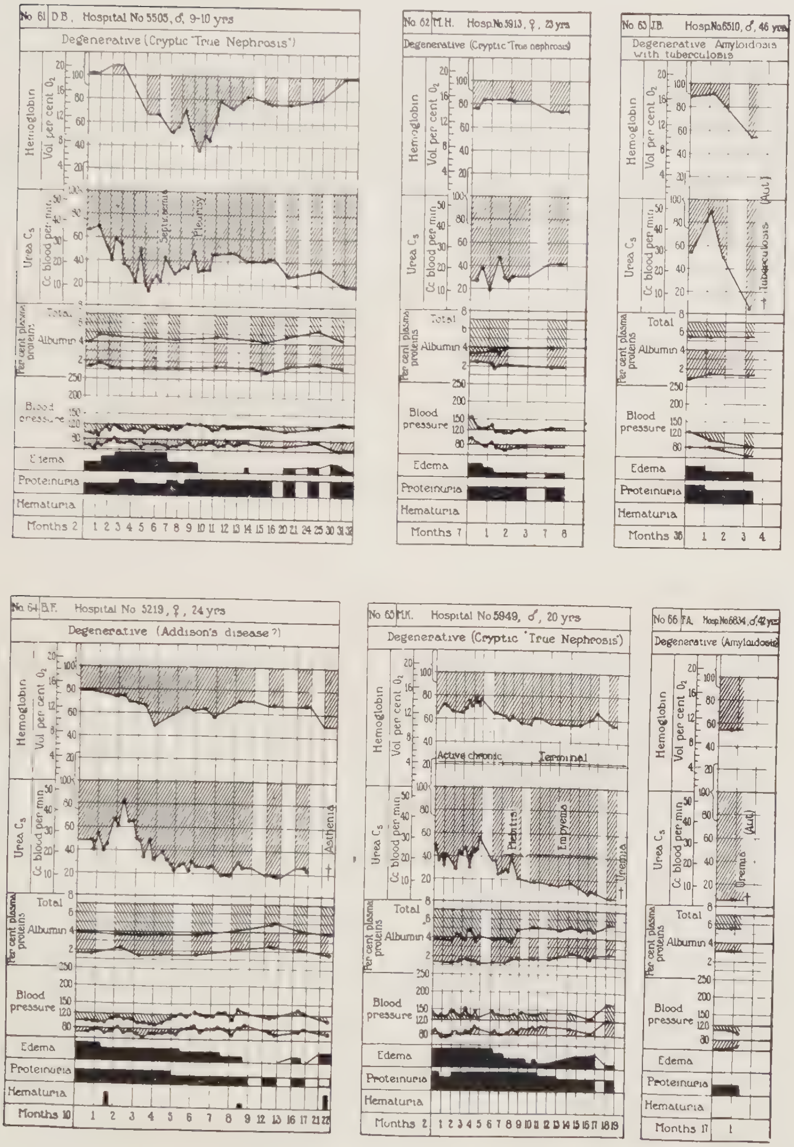
In every one of our cases the plasma albumin content was below 2.5 per cent on admission, and total proteins were below 5.5 per cent, usually below 5.0.

The cases are arranged, as in the previous groups, in order with those of apparently most favorable clinical outcome, in so far as the disease is concerned, first in the series.

The first 3 cases are the only ones that showed definite and significant rises in total protein and albumin content during the course of observation. Of these no. 57 made an apparently complete recovery and returned to the normal activities of a boy of his age. His plasma proteins returned completely to normal level 2 years after observation was begun, and 2 and $\frac{3}{4}$ years after symptoms of the disease were first noted. Case 58 left the hospital subjectively well, and apparently on the road to ultimate recovery. Case 59, of 16 years duration, improved in 1 year from a condition of complete helplessness to one in which he could walk indoors and out and begin to renew relatively sedentary activities. During this period of improvement the plasma albumin rose from 0.9 to 2.8 per cent, passing the critical level previously discussed, and edema became relatively manageable. There was a fall in plasma albumin and some increase in edema during a period of a month's absence from the hospital. The streptococcus infection terminated a case which had begun to arouse hopes of a cure like that of no. 57.

In none of the other cases (nos. 60 to 65 inclusive) did the plasma albumin rise above 2.5 per cent, and in none of them was there a permanent disappearance of the edema.

No. 66 represents an exception among pure degenerative cases, in that the edema was never severe. Even without treatment it had increased the body weight only by a few pounds. The subjective symptoms were those of a terminal hemorrhagic case rather than those usually typical of nephrosis. In accordance with these observations there was found a uremic nitrogen retention, but only a moderate plasma protein deficit, the albumin being 3 per cent and the total 5.5.


No 61 D.B. Hospital No 5505, ♂, 9-10 yrs
Degenerative (Cryptic "True Nephrosis")
Septicemia
Pleurisy
Months 2 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 20 21 24 25 30 31 32
No 62 M.H. Hosp.No.5913, ♀, 23 yrs
Degenerative (Cryptic "True nephrosis")
Months 7 1 2 3 7 8
No 63 J.B. Hosp.No.6510, ♂, 46 yrs
Degenerative Amyloidosis with tuberculosis
† Tuberculosis (Aut.)
Months 36 1 2 3 4
No 64 B.F. Hospital No 5219, ♀, 24 yrs
Degenerative (Addison's disease?)
Asthenia †
Months 10 1 2 3 4 5 6 7 8 9 12 13 16 17 21 22
No 65 M.K. Hospital No 5949, ♂, 20 yrs
Degenerative (Cryptic "True Nephrosis")
Active chronic
Terminal
Pleuritis
Empyema
Uremia †
Months 2 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
No 66 F.A. Hosp.No.6834, ♂, 42 yrs
Degenerative (Amyloidosis)
Uremia † (Aut.)
Months 17 1
Hemoglobin
Vol per cent O₂
20 16 12 8 4
100 80 60 40 20
Urea Cs
Cc blood per min
50 40 30 20 10
100 80 60 40 20
Per cent plasma proteins
Total
Albumin
8 6 4 2
Blood pressure
250 200 150 120 80
Edema
Proteinuria
Hematuria

CHARTS 61-66

The case was diagnosed nevertheless as nephrosis because of the consistently low blood pressure and the absence of microscopic hematuria. Autopsy showed a typical amyloid nephrosis.

The relatively moderate albumin deficit is not characteristic of amyloid nephroses: they usually show deficits equal to those of lipoid nephrosis. Case 63 for example, showed the usual marked deficit. No. 66, however, demonstrates that it is possible for exceptional pure degenerative Bright's disease, at least of the amyloid type, to occur with only moderate plasma protein loss and edema.

Proteinuria was marked in all cases, the output varying from 2 grams per day to over 20 grams.

Edema was present in all cases, except no. 66, in which the plasma albumin was relatively high. Elimination of edema in cases 57, 58, 59 and 64 occurred under the combined effect of treatment and increase of plasma albumin. In cases 60, 61 and 62 edema diminished or disappeared temporarily under the influence of treatment without increase in plasma albumin.

The data regarding *anemia* have already been sufficiently discussed above.

ANATOMICAL CHANGES OBSERVED IN DEGENERATIVE BRIGHT'S DISEASE (CASES 59, 63, AND 66)

Nephroses include, according to Fahr (1925), all primary degenerative diseases of the kidneys which attack the glomeruli and the tubules, but not those which attack the vascular system. Fahr separates from the plain nephroses a group in which, besides degenerative lesions, infiltrative changes occur, which, according to him, are due to disturbances in metabolism. This group he called the definitely characterized nephroses, and classifies with them the so-called lipoid and amyloid nephroses. Aschoff (1921), on the contrary, does not believe that these two diseases are of the same nature, but ascribes amyloid nephrosis, which he calls amyloid infiltration, to nephrodystrophies, and lipoid nephrosis to inflammations of the kidneys, calling it tubular nephritis. Aschoff (1913, 1917) also objects to the term nephrosis and logically argues that this term should be replaced by "nephrodystrophia" or "nephropathia." If here, nevertheless, we use the term, nephrosis, it is because it is generally accepted by clinicians, and especially because no agreement has yet been reached concerning the nature of this disease. For similar reasons we also discuss here the amyloid and lipoid forms together, because they resemble each other in many respects, not only clinically, but also anatomically.

Lipoid nephrosis. Case 59 has been reported in detail elsewhere (Ehrich, 1929). Here we shall, however, discuss it briefly. Macroscopically, we found large white kidneys without visible blood dots. Histologically, an intense fatty and hyaline-droplet degeneration of the epithelial cells was outstanding, in comparison with which all other changes were insignificant. There was indeed marked scar formation and hyalinization of half of the glomeruli. But most of the preserved glomeruli were intact. Only in a few glomeruli increased numbers of nuclei were seen. But this increase was not out of proportion to the size of the glomeruli. In some hyalinized glomeruli there were slight proliferations of the parietal epithelial cells. All these lesions are found, according to Fahr (1918, 1922) and others, more frequently in advanced cases of lipoid nephrosis. Furthermore, if we take into consideration the clinical observations, there can be no doubt of the diagnosis "genuine lipoid nephrosis."

Of special interest was the fact, that, in spite of a duration of about 17 years, no shrinkage of the kidneys had occurred. Whereas Fahr (1925) and others believe that lipoid nephrosis leads to contracted kidneys, Aschoff (1913) and others express doubt. That amyloid nephrosis may lead to contracted kidneys is no wonder, if we take into consideration the great destruction of glomeruli, which is generally assumed to lead to contraction. However, in lipoid nephrosis, the conditions are quite different. Here, the glomeruli are much less diseased and there is no extensive destruction of them. There appears to be in the literature no case of contracted kidney which can with certainty be ascribed to pure lipoid nephrosis (Ehrich, 1929). Our case, which seems to be the only genuine one of such long duration observed, shows that prolonged lipoid nephrosis does not necessarily lead to contracted kidneys.

Amyloid nephrosis. Whereas lipoid nephrosis is only rarely observed in autopsy, amyloid nephrosis occurs frequently. Concerning its morphological course Volhard and Fahr (1914) have distinguished three stages and Fahr later on (1925) four stages, for the purpose of facilitating description.

Case 63 showed lesions characteristic of the second stage. Besides amyloid infiltration, severe degenerative changes were found. Both kidneys were very large. The glomeruli still contained many loops filled with blood. A slight scar formation was present. The changes of the tubules were essentially the same as those in lipoid nephrosis.

Case 66 we ascribed to the third stage, because a marked scar formation had already developed and because the amyloid no longer gave the iodine sulfuric acid reaction, whereas the methyl violet reaction in part was still positive. The glomeruli were greatly infiltrated with amyloid. Most of the glomeruli contained no erythrocytes. The destruction of the glomeruli and arterioli was so extensive that a renal insufficiency and uremia developed. The tubules were in the stage of advanced atrophy, whereas fatty and hyaline-droplet degeneration were insignificant.

Our cases of amyloid nephrosis were of special interest also from the etiological point of view. Whereas the amyloidosis of case 64, as so frequently occurs, was due to tuberculosis, in case 66, in spite of thorough examination, no visible cause could be found. Examination of the bones at autopsy was not permitted. But, because no clinical symptoms were present, we believe we can exclude a bone disease with certainty. Nor can the old healed endocarditis, which was found in this case, be held responsible for the amyloidosis. We have to place this case, with a number of others reported in the literature (cf. Fahr, 1925), in the group of unknown etiology.

CASE HISTORY ABSTRACTS AND AUTOPSY REPORTS. DEGENERATIVE BRIGHT'S DISEASE (CASES 57 TO 66)

Case 57. Hospital No. 4616. B. S., male, 11 years. *Degenerative Bright's disease. Progressing to cure.*

Ten months before admission the patient had sore throat. Three weeks later he had swelling of face and neck, and albuminuria was found. Spent 6 weeks in Bronxville hospital, then 4 months in bed at home. Then returned to school. Swelling of face increased. There were no constitutional symptoms nor hematuria.

On admission tonsils and adenoids were found enlarged. Heart was slightly enlarged, without valvular disease. Blood pressure was 95/70. There was swelling of face and ankles. The urine contained 4 grams of albumin per liter, a few epithelial cells, granular casts, hyaline casts, and white cells. Very few red cells were found on 2 occasions in first 3 weeks. Edema quickly cleared up. Diseased tonsils and adenoids were removed. Edema tended to recur, and was combatted with urea administration, which he continued to take at home, 3 months after admission. Returned to hospital 16 months after first admission with massive general edema. While patient was under observation catarrhal otitis media developed. At the same time the edema disappeared, and albuminuria decreased. Two months later only faint traces of albumin remained. Subsequent observations showed the urine free of albumin and cellular elements.

Case 58. Hospital No. 5644. F. O., male, 24 years. *Degenerative Bright's disease.* Syphilis.

Since the age of 18 the patient has had chronic periostitis of both tibiae. A ++++ Wassermann reaction was found, and several treatments with salvarsan and mercury were given with good effect. Eight to 9 months before admission, during such treatment, edema appeared. Four months before admission a gangrenous appendix was removed.

On admission a typical luetic tibial periostitis and signs of a previous keratitis were found. The urine sediment contained no erythrocytes, some leucocytes and double refracting bodies, and many hyaline and granular casts. The eyegrounds, blood pressure, ahd heart size were normal. Wassermann reaction negative. Blood urea nitrogen 45 mgm. per cent. Blood creatinine 1.71 mgm. per cent.

The plasma albumin increased to 2.96 per cent and edema gradually disappeared. Since 16 months after admission the patient had been doing a full day's work and eating an ordinary diet. The Wassermann reaction is still negative. The sediment still contains a few hyaline and granular casts.

Case 59. Hospital No. 6184. M. M., male, 17 to 18 years. *Degenerative Bright's disease of 17 years' duration* → exitus.

The patient was apparently well at birth. At age 16 months onset of present illness occurred with facial edema and albuminuria. For 14 years he was on a low protein and salt-free diet and continued to excrete large amounts of albumin. He has had recurrent attacks of edema every two years lasting 2 to 3 weeks until the present attack, which had its onset 2 years and 5 months before admission. He was treated for this with high protein diet, tonsillectomy and several tooth extractions. Owing to edema and time in bed, severe contractures of posterior muscle groups of both legs were present.

On admission he was pale, edema of extremities was pronounced; he had marked ascites, several badly decayed teeth, and distinct anemia (hemoglobin 11.6 volume per cent O_2). Cholesterol was 272 mgm. per cent, plasma albumin was only 0.9 per cent, globulin 3.39 per cent. The urine sediment contained many hyaline and granular casts, occasional red blood cells. Albumin excretion in urine averaged 6 to 9 grams per day. The blood pressure was 108/78. Renal function was slightly subnormal.

Over a course of 9 months the patient was on a high protein and salt-free diet. During this time most of the edema disappeared, and the contractions of legs were reduced to extent that he could walk unaided. The albumin rose to 2.8 per cent; globulin remained about the same level at 3.2. The plasma cholesterol fell to 187 mgm. per cent. During the entire course under observation the blood pressure remained low.

Patient was readmitted after one month because of slight increase of edema of legs and puffiness about the eyes. Subjectively well. Two weeks later the onset of general peritonitis (hemolytic streptococcus) was marked by a chill, a rise of temperature to 105°, and abdominal pain. December 2, 1928, death occurred from general peritonitis.

Autopsy. Autopsy No. 311/1928. We were only permitted to do a partial autopsy, limited to the kidneys. This was performed about 2 hours after death.

Each kidney weighed about 300 grams. The capsule stripped easily. The surface was pale yellowish in color and smooth, with indications of fine light violet shadings. Blood dots could not be found. On cross section (fig. 33) the cortex was much enlarged, measuring from 9 to 20 mm. It was pale yellowish in color and contained fine radiate light violet stripes. The cortex was fairly well marked off from the medulla. In the pelvis a few hemorrhages were seen.

Microscopic examination. The cortex contains stripes and patches of enlarged tubules (fig. 34) the character of which as convoluted tubules is still distinct in many places. In places these tubules are lined by *much swollen epithelial cells that have undergone fatty or vacuolic degeneration* (fig. 35) closing the tubules partly or entirely. In places the latter are lined by epithelial cells *far gone in hyaline-droplet degeneration.* The epithelial cells, mainly of these degenerated tubules, frequently contain pycnotic nuclei or have lost nuclei entirely. In many instances the epithelial cells are desquamated. In such places one finds signs of regeneration (fig. 36). Gaps in the epithelial layer are covered by endothelium-like epithelial cells, some of which contain karyokinetic figures. In the basal parts of the epithelial cells one sees nearly everywhere fine-grained fat (fig. 35) which mostly is

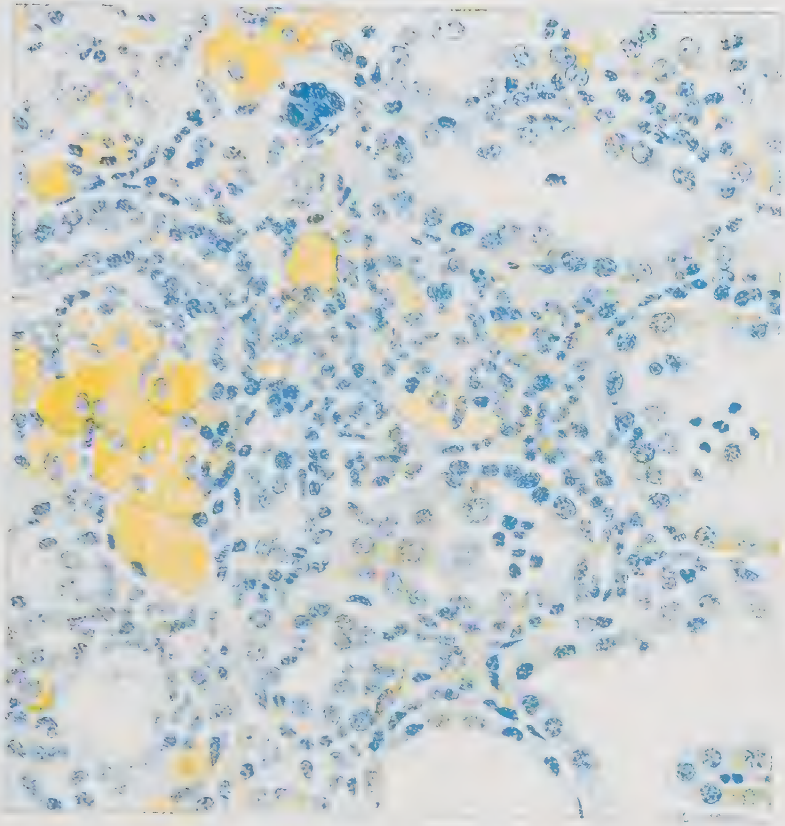


FIG. 35. Case 59. For diagnosis see figure 33.

Xanthoma-like lipoid cells in the interstitial tissue. Fatty degeneration of the convoluted tubules in the lumina of which one sees desquamated epithelial cells and polymorphonuclear leucocytes. Mueller-formalin fixation, Sudan III-hematoxylin. ×400.

doubly refractive. Within the lumina of the tubules one finds coagulated protein, some desquamated epithelial cells, and in some places also polymorphonuclear leucocytes (figs. 35 and 36). The minor parts of the tubules contain fairly large numbers of casts which increase in number towards the medulla. The interstitial tissue of these parts of the cortex appears to be normal in most places.

In other parts of the cortex, the interstitial tissue is frequently enlarged and contains increased collagenous connective tissue. In places there are small round cell infiltrations, some of which are adjacent to hyalinized glomeruli. In other places, the interstitial tissue is swollen and penetrated by polymorphonuclear leucocytes which frequently enter the tubules. Everywhere in the interstitial tissue of these parts of the cortex one finds large, xanthoma-like cells, which are stained yellowish by Sudan (fig. 35), and which are doubly refractive. The tubules of the scarred parts are in all stages of atrophy and degeneration up to entire disappearance. Their epithelial cells are much more desquamated than those of other parts of the cortex. They frequently contain a large amount of fat which is very irregularly arranged. Occasionally one sees signs of regeneration. In some places one finds calcified casts.

Half of the glomeruli are well preserved (fig. 34), partly of normal size and *partly enlarged.* The enlarged glomeruli contain increased numbers of nuclei, but the increase is proportional to the size of the glomeruli. In a few places one finds small accumulations of endothelial cells in a single tuft. The tufts of the well preserved glomeruli are delicate and mostly well filled with blood. Occasionally, the capsule spaces are dilated and contain coagulated protein. There is little fat to be found in the covering cells of the glomeruli. Nowhere in these glomeruli does one see typical inflammatory lesions.

The other half of the glomeruli are in all stages of hyaline degeneration. In some otherwise well preserved glomeruli the capsules are concentrically thickened. Other glomeruli contain hyalinized tufts, especially at the entrances of the vessels; occasionally the tufts are adherent to the capsules. A few of these glomeruli show a slight proliferation of the parietal epithelial cells, but nowhere crescent formations. About one-third of the glomeruli are entirely hyalinized and are sharply separated from their surroundings.

The medulla is rich in collagenous connective tissue, which is swollen in places and contains some polymorphonuclear leucocytes and swollen round cells. In the tubules of the medulla numerous casts are seen, and in one place also some erythrocytes. The arterioli are well preserved. The larger

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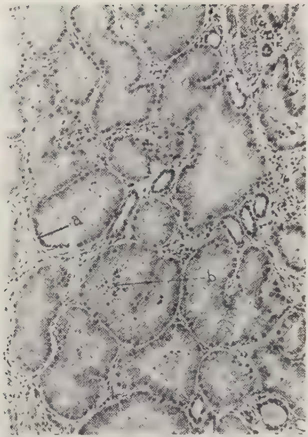

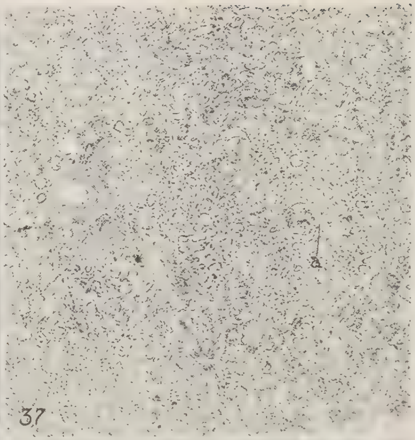

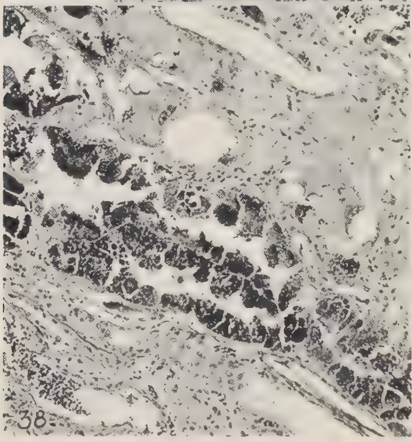

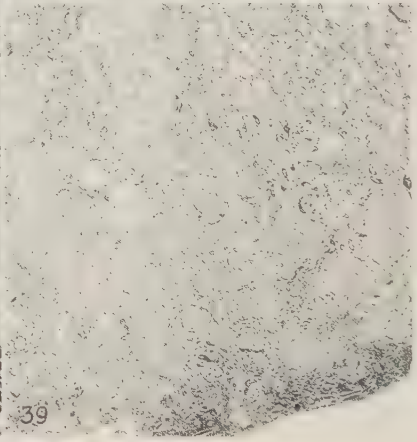

Fig. 36. Case 59. For diagnosis see figure 33.

Regeneration in a gap of the epithelial layer (*a*). In the lumina of the tubules coagulated protein and some polymorphonuclear leucocytes (*b*). Mueller-formalin fixation, iron-hematoxylin-eosin. ×160.

Fig. 37. Case 63. Anatomical diagnosis: amyloid nephrosis, State II. Clinical diagnosis: non-hemorrhagic degenerative Bright's disease and tuberculosis.

Marked amyloidosis of the glomeruli and arterioli (*a*). Fatty and hyaline-droplet degeneration of the convoluted tubules. Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

Fig. 38. Case 63. For diagnosis see figure 37.

Extensive hyaline-droplet degeneration of some tubules. Mueller-formalin fixation, Gram. ×200.

Fig. 39. Case 66. Anatomical diagnosis: amyloid nephrosis. Stage III. Clinical diagnosis: non-hemorrhagic degenerative Bright's disease with renal failure.

Extensive diffuse amyloidosis of the glomeruli, arterioli, and arteries. Scar formation below the capsule with round-cellular infiltrations. Atrophy and degeneration of the tubules with numerous casts. Mueller-formalin fixation, iron-hematoxylin-eosin. ×60.

arteries show a moderate degree of intimal hyperplasia. All amyloid reactions are negative.

Anatomical diagnosis. Lipoid nephrosis.[5]

Case 60. Hospital No. 5159. M. R., male, 30 years. *Degenerative Bright's disease.*

Sixteen months before admission edema and albuminuria appeared and have remained since then.

On admission the urine sediment congained no erythrocytes but some hyaline and granular casts. The eyegrounds, blood pressure and heart size were normal. Wassermann reaction was negative. Plasma globulin is 2.62 per cent, albumin 2.17 per cent, blood urea nitrogen 19 mgm. per cent, blood creatinine 1.57 mgm. per cent, plasma cholesterol 417 mgm. per cent, basal metabolic rate −30.6 per cent.

During stay in hospital the urine sediment usually contained many hyaline and granular casts. The plasma albumin varied between 1.62 and 2.19 per cent. The other findings were unchanged, up to the time of discharge. Subsequent examinations, made 13 months and 16 months afterwards showed little change.

Case 61. Hospital No. 5505. D. B., male, 9 to 10 years. Height 134 cm. *Degenerative Bright's disease.*

Two months before admission the patient had a slight cold followed by swelling of the face and legs and by albuminuria.

On admission the urine sediment contained hyaline and granular casts and a few leucocytes and doubly refractive bodies. The eyegrounds, blood pressure and heart size were normal. Chronic tonsillitis was present but no sinusitis. Wassermann reaction was negative. Plasma globulin was 2.52 per cent, albumin 1.31 per cent, blood urea nitrogen 32 mgm. per cent, blood creatinine 1.23 mgm. per cent, total fat in plasma 1.32 per cent and the basal metabolic rate −13.5 per cent.

These findings did not change significantly during the period of observation except for the sediment, which, when the patient was last seen, 20 months after admission, contained no casts but still some leucocytes. At this time the patient was going to school and in good condition. He is still taking a salt-free diet. The septicemia 6 months after admission was caused by pneumococcus Type IV.

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[5] A more detailed description and discussion of this case see in MacKay and Johnston, (1930), and Ehrich (1930).

Case 62. Hospital No. 5913. M. H., female, 23 years. *Degenerative Bright's disease.* Complicated by pregnancy.

Seven months before admission albuminuria was accidentally found. One month later she became pregnant and during the next month edema appeared. An abortion was provoked, but the edema persisted.

On admission the urine sediment contained no erythrocytes, some leucocytes and hyaline casts, and many granular casts. The eyegrounds, blood pressure and heart size were normal. Wassermann reaction was negative. Plasma globulin 1.88 per cent, albumin 1.88 per cent, blood urea nitrogen 36 mgm. per cent, blood creatinine 1.51 mgm. per cent, plasma cholesterol 536 mgm. per cent, basal metabolic rate −16 per cent.

During observation the number of casts decreased considerably. The plasma albumin increased to 1.94 per cent. The patient is still taking a salt-free diet.

Case 63. Hospital No. 6510. J. B., male, 46 years. *Degenerative Bright's disease (amyloid) with tuberculosis*→exitus.

For 3 years before coming to hospital, the patient had had severe gastrointestinal symptoms. Six months before admission edema of the feet and legs had appeared and he was told that he had Bright's disease because of the finding of albumin in the urine. He had lost 20 pounds in weight during the 3 months previous to the onset of edema. At no time had there been gross hematuria.

On admission there were signs of advanced pulmonary tuberculosis. The blood pressure measured 120 mm. systolic and 80 mm. diastolic. The urine contained about 18 grams of protein per day, many hyaline casts, double refractive bodies, and many white blood and epithelial cells; no red blood cells were observed in the sediment. The blood urea N was 17.1 mgm. per cent, and the plasma NPN was 36 mgm. per cent. The albumin fraction of the plasma proteins was only 0.87 gram per 100 cc. The globulin was increased to 4.4 per cent. The blood hemoglobin was 16.5 volumes per cent O_2 capacity. A phenolsulfonephthalein test resulted in a 70 per cent return of the dye in 2 hours.

During the $3\frac{1}{2}$ months that the patient was under observation, the pulmonary lesion increased. Evidence of degeneration in the kidneys continued: the protein excretion in the urine remained above 20 grams per day, and the excretion of white blood and epithelial cells and casts increased. Excretion of red blood cells did not occur. The plasma proteins remained low, as did the blood pressure. The phthalein excretion was reduced to 38 per cent in 2 hours. The blood urea nitrogen did not rise above 27 mgm. per cent. The development of intestinal tuberculosis lesions, during the second month that the patient was in the hospital, hastened death.

Autopsy. Autopsy No. 313/1928. We were permitted to do only an autopsy of the abdominal cavity. This was performed 13 hours after death.

Death by chronic pulmonary and ulcerous intestinal tuberculosis. Extended amyloidosis was present also in the kidneys, in liver, spleen, adrenals and intestine.

The right kidney weighed 210, the left 220 grams. Both kidneys were firm. Their capsules stripped easily. The surface of each was smooth and yellowish gray in color. The cortex was enlarged and similar in color to the surface. It was well marked off from the brown red medulla.

Microscopic examination. All glomeruli are more or less diseased. In each glomerulus all or part of the loops are infiltrated with amyloid in diffuse distribution (fig. 37). The amyloid gives a positive iodine sulfuric acid reaction as well as a positive methyl violet reaction. Frequently the glomeruli contain tufts well filled with blood. There is no fat within the glomeruli. Occasionally one finds increase in the number of nuclei in some tufts. The parietal epithelial cells are increased in number in some instances.

Nearly all arterioli are changed in to thick amyloid tubes (fig. 37), the lumina of which are open in most places. Occasionally they contain fat. The larger arteries contain only a little amyloid and show slight degree of intimal hyperplasia.

The tubules of the cortex are markedly changed. The *proximal tubules* are enlarged and lined with greatly swollen epithelial cells which in places close the lumina entirely. The epithelial cells have undergone degeneration, which is partly of the fatty, partly of the hyaline-droplet type (fig. 38). Frequently they contain pycnotic nuclei or have lost them entirely. In many instances the epithelial cells are desquamated. In such places there are signs of regeneration. In the basal parts of the epithelial cells one sees nearly everywhere fine or coarse grained fat, part of which is doubly refractive. Also the *distal parts* of the tubules contain in places much fat. In the lumina of the tubules one finds some coagulated protein, many swollen and desquamated epithelial cells, and in some places also polymorphonuclear leucocytes. Everywhere they contain numerous casts.

The interstitial tissue is well preserved. In a few places small scars are seen which may contain small round cellular infiltrations.

Anatomical diagnosis. Amyloid nephrosis (Stage II of Fahr).

Case 64. Hospital No. 5219. B. F., female, 24 years. *Degenerative Bright's disease* → exitus.

Ten months before admission edema gradually appeared, followed by loss of strength and appetite. Two months before admission the patient had pleurisy for 3 weeks.

On admission marked asthenia and some abnormal increase in skin pigmentation was found. The urine sediment contained some leucocytes and hyaline casts. The eyegrounds were normal except for pigmentation. The blood pressure was 98/76. The heart was a "drop-heart." A test meal showed achylia gastrica. Wassermann reaction negative. Plasma globulin was 2.08 per cent, albumin 1.77 per cent, blood urea nitrogen 25 mgm. per cent, blood creatinine 1.27 mgm. per cent and the basal metabolic rate 11.0 per cent.

During observation the urine sediment showed an increasing number of granular casts. Occasionally doubly refractive bodies were found, but never any erythrocyte casts. The blood pressure remained abnormally low until 5 months after admission; it then rose to about 125/80, but decreased again during the last 8 months of observation. Diarrhoea was often present, and anorexia and asthenia most of the time. Amenorrhoea was present during a period of 5 months. The plasma albumin gradually increased to about 2.4 per cent, but one week before death it wa only 1.82 per cent. Five months after admission the blood urea nitrogen began to rise. One week before the death the blood urea nitrogen was 211 and the creatinine 9.1 mgm. per cent. Death occurred in asthenia ffter a period with diarrhoea and oliguria. The day before death the blood pressure was 66/38. No autopsy. Addison's disease was suspected.

Case 65. Hospital No. 5949. M. K., Male, 20 years. *Degenerative Bright's disease* → uremia → exitus.

For several years he had a chronic infection of the nose. This practically ceased after an operation 5 months before admission. Eight months before admission edema and ascites appeared. Three months later albuminuria was found, but the blood pressure and blood urea nitrogen were normal.

On admission the urine sediment contained a few erythrocytes, some leucocytes, many granular and cellular casts, and occasional doubly refractive bodies. The eyegrounds, blood pressure, and heart size were normal. Wassermann reaction negative. Plasma globulin was 2.47 per cent, albumin 1.30 per cent, blood urea nitrogen 35 mgm. per cent, blood creatinine 1.46 mgm. per cent, plasma cholesterol 877 mgm. per cent, and basal metabolic rate −28.2 per cent.

During observation the plasma albumin decreased further to a minimum of 1.17 per cent and then rose gradually to 1.80 per cent. The plasma cholesterol decreased and was 226 mgm. per cent 9 months after admission. The urine sediment and blood pressure had not changed significantly. The blood urea nitrogen increased to 99 mgm. per cent, the blood urea clearance fell to values characteristic of the terminal stage and death followed in uremia. No autopsy.

Case 66. Hospital No. 6834. F. A., male, 42 years. *Degenerative Bright's disease (amyloidosis) → uremia →* exitus.

The patient passed an insurance examination 3 years before admission and was told he had abnormally low blood pressure at that time. Onset 17 months before admission with weakness. Edema appeared 5 months later. There had been no gross hematuria noted. From 2 months previous to admission there had been severe abdominal cramps, also intermittent diarrhea.

On admission to hospital the patient was in uremia. The blood urea nitrogen was 86.1 mgm. per cent. Non-protein nitrogen 115 mgm. per cent. The phenolsulphonephthalein test resulted in less than 1 per cent return in 2 hours. The blood pressure was 110/55. The plasma albumin was somewhat reduced to 3.1 per cent, the globulin remaining normal at 2.7 per cent. A fresh specimen of urine revealed by ordinary microscopic examination no red blood cells. However, a concentrated 12-hour specimen showed 1,600,000 red blood cells (normal limit = 500,000), 27,000,000 white blood cells and epithelial cells, and 600,000 casts, 10 per cent of which were of Addis' renal failure type, 5 per cent hyaline, 5 per cent epithelial, and 80 per cent granular in character. The protein excretion in the urine was 3.5 grams daily. While under observation, the patient's condition became rapidly worse, and he died of uremia on the tenth day. The blood pressure remained low to the end; the systolic measured between 90 and 110 mm. and the diastolic between 55 and 78 mm.

Autopsy. Autopsy No. 317/1929. Autopsy commenced 8 hours after death.

Death in uremia. Uremic hemorrhages in the intestine. Extended amyloidosis, in the kidneys, liver, lung, adrenals, pancreas, spleen and intestine. Fresh serofibrinous pericarditis. Old healed endocarditis of the mitral and aortic valves. Moderate atheromatosis of the aortic cusp of the mitral valve, of the coronary arteries and of the aorta. An etiologic cause for the amyloidosis could not be found.

The right kidney weighed 160, the left 170 grams. The capsule of each stripped easily. Both kidneys were remarkably flabby. The cortex was yellowish gray in color and finely granulated. Hemorrhages were not seen. The cortex was of about normal breadth, yellowish gray in color and faded. It was well marked off from the medulla.

Microscopic examination. The glomeruli are of about normal size.

Frequently, they fill out the capsules entirely. *Their tufts are greatly infiltrated with amyloid in diffuse distribution* (figs. 39 and 40). The amyloid no longer gives iodine sulfuric acid reaction, but does give a positive methyl violet reaction in many places. Only a few glomeruli still contain blood. Most of the glomeruli do not show any erythrocytes. Many tufts are poor in nuclei. Many glomeruli contain much fat in their tufts (fig. 41). The parietal epithelial cells are occasionally increased in number. Single glomeruli are hyalinized and stained red by Van Gieson.

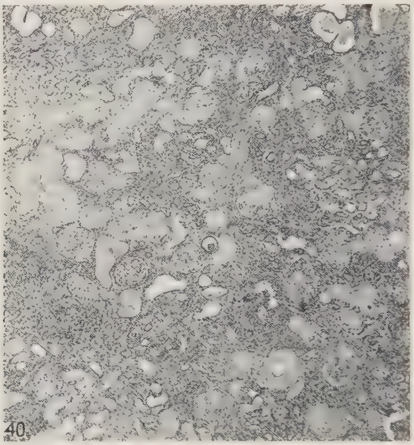

Fig. 40. Case 66. For diagnosis see figure 39.
Extensive diffuse amyloidosis of the arteries, arterioli, and glomeruli. Distinct scar formation in the interstitial tissue. Atrophy and degeneration of the tubules. In the tubules many casts. Mueller-formalin fixation, elastica-Van Gieson. ×60.

Nearly all arterioli are changed into thick amyloid tubes (figs. 39 and 40), the lumina of which are narrowed or closed entirely. Frequently they contain fat. Also the larger arteries are much infiltrated with amyloid. In most places all layers of the walls are affected. However, the largest amount of amyloid is found in the adventitial layer. Occasionally, the media is fairly well preserved. The intima of the larger arteries is hyperplastic in some instances and contains fat.

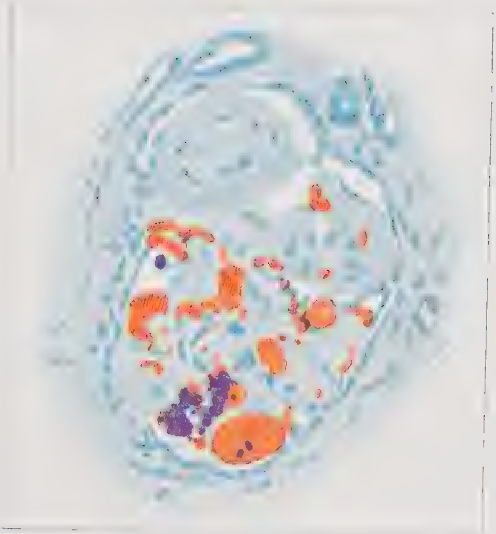

FIG. 41. Case 66. For diagnosis see figure 39.

The tufts of the glomerulus are infiltrated by amyloid and fat. Some of the loops contain dark-blue stained grains (calcium?). The afferent arteriole is entirely changed to amyloid matter. Mueller-formalin fixation, Sudan III-hematoxylin. ×200.

Also in the interstitial tissue of the kidneys, especially of the medulla, diffuse amyloid is found.

The tubules are in the stage of advanced atrophy up to entire disappearance. Frequently, they are dilated and their epithelial cells flattened so that it is often difficult to differentiate ascending and descending tubules. Occasionally, the epithelial cells contain fat which is very irregularly arranged. Vacuolic degeneration is distinct in some places, but as a slight hyaline-droplet degeneration, not very conspicuous. The epithelial cells are frequently desquamated. Occasionally one sees signs of regeneration. In the lumina of the tubules one finds coagulated protein. Of the epithelial cells some are desquamated and some have undergone fatty degeneration. In a few places there are polymorphonuclear leucocytes. Everywhere the tubules contain large numbers of casts.

The interstitial tissue of the kidneys is frequently enlarged and contains increased collagenous connective tissue. In such scars one sees round cell infiltrations (fig. 39). In a few interstitial places one finds some polymorphonuclear leucocytes entering the tubules. The capillaries are in part well filled with blood.

Anatomical diagnosis. Amyloid nephrosis (Stage III of Fahr).

SUMMARY

Clinical, chemical and functional observations, continued for periods varying from a few weeks to several years, are reported on 67 patients with Bright's disease, hemorrhagic, sclerotic, and degenerative. Gross and microscopic anatomical findings are described for 17 of these cases.

Our observations support the view of Volhard and Fahr and of Addis that the three types of Bright's disease are essentially different in their genesis and pathological nature: the hemorrhagic or glomerular, marked primarily by glomerular inflammation, with hematuria and usually diminished renal function (even in the acute stage); the sclerotic disease, marked primarily by pathological changes in the small arteries of the kidneys (and usually other organs), with hypertension as the first sign and diminished renal function only as a terminal phenomenon; the degenerative disease or diseases, called nephrosis, marked primarily by degenerative changes in the kidneys, without hypertension and with hematuria. Contrary to the apparently general belief, except that of Addis, we have observed that gradual decrease of urea excreting ability frequently develops during the course of nephrosis, and that the disease may end in uremia, the glomeruli being then involved in the degenerative changes.

Our data also support the belief of Volhard and Fahr and of Addis that it is possible from observations during the course of the disease to deduce the general nature of the pathological changes occurring in the kidneys. In the cases clinically diagnosed as hemorrhagic nephritis and examined post-mortem, the changes characteristic of glomerular inflammation were outstanding, except in some diagnosed as hemorrhagic plus arteriosclerotic, in which it was difficult to tell histologically whether the glomerular or arterial changes were primary. In the cases diagnosed as arteriosclerotic and as degenerative Bright's disease (nephrosis) the post-mortem findings were confirmatory. The clinical differentiation between lipoid and amyloid nephrosis was not attempted.

The diagnoses have been made chiefly on the basis of observations of the urea excreting power of the kidneys, measured by the blood urea clearance (cubic centimeters of blood cleared of urea by 1 minute's excretion, Moeller, McIntosh, and Van Slyke (1928)), of the hematuria, blood pressure, plasma protein content, proteinuria, and edema. Blood hemoglobin content was also followed, and although not of decisive diagnostic value was found to be of interest as an indication of the toxic damage suffered by the organism, and to have prognostic significance. The above observations are presented in charted form for each patient.

In acute hemorrhagic nephritis the prognosis was found to be independent of the severity of the disturbances during the first weeks, with the single exception of the plasma albumin content. The majority of cases in which this fell to a low level became chronic. Intensity of hematuria, proteinuria, and degree of hypertension had no apparent relation to the probability of recovery. Fall of the renal function to as low as 10 per cent of normal, measured by the blood urea clearance, was found not inconsistent with apparently complete recovery. The majority of cases showed during the first two months a decided fall in renal function measured by the blood urea clearance. In all these cases which recovered or improved, however, the blood urea clearance began to rise within 4 months after the acute hemorrhagic onset. The occurrence or non-occurrence of this rise in renal function constituted the most definite single prognostic sign.

After the initial acute stage of hemorrhagic nephritis a period was observed in some cases during which hematuria and hypertension quite disappeared, while proteinuria, plasma protein deficit, and edema still persisted. During this stage, these cases, except for their acute hemorrhagic history, were indistinguishable from nephrosis. Subsequently in a few months, however, they either completed recovery or improvement to the symptom-free latent stage, either of which was a relatively rare occurrence in our nephrosis cases, or else they developed into chronic hemorrhagic nephritis.

The tendency to non-cardiac edema was found to parallel approximately the fall in albumin content of the blood plasma, except during the first weeks of acute hemorrhagic nephritis. Edema during this period was repeatedly observed even when the plasma proteins remained normal. The edema was, however, moderate and temporary unless plasma albumin deficit developed. In all stages of nephrosis plasma albumin deficit and tendency to edema occurred together. One case of amyloid nephrosis, the diagnosis of which was checked by autopsy, was exceptional in that edema had been present to only a slight extent: in this case the plasma albumin showed only a relatively moderate fall below normal. In arteriosclerotic renal disease plasma proteins were never markedly reduced, and only cardiac edema was observed.

Of the different features of the disease that were followed, the blood urea clearance proved to be the most closely related to the onset of final renal failure. The renal function, measured by the clearance, could apparently remain indefinitely at 10 per cent of normal without uremia; but when it fell to below 5 per cent uremia occurred and was usually fatal. Exceptions to the immediately fatal outcome were found in acute cases, which can recover if the functional depression does not last too long, and occasionally a terminal case, in which the functional fall is partly due to factors, such as desiccation, other than destruction of renal tissue. In such a case treatment, particularly saline and glucose injections, may both improve general condition and somewhat increase the blood urea clearance, although the added lease of life appears to be at most a few months.

The above summary indicates only incompletely the nature of the observations reported. The variations within each of the 3 types of

Bright's disease studied are great, and a study in detail of the case examples presented is necessary for utilization of the material concerning the incidence, intensity, time relationships, and diagnostic and prognostic significances of the functional and chemical disturbances that have been studied.

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STUDIES ON THE BACTERIOLOGY OF EPIDEMIC INFLUENZA[1]

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It is now six years since I first came here to demonstrate the work done by Dr. Gates and myself on the bacteriology of epidemic influenza. The presentation (1) was then made under the egis of Dr. Charles E. Simon, at the beginning of his series of courses on Filterable Viruses. The courses were notable not only because they were the first to be given on this subject in a special department of a school curriculum, but also because they were comprehensive and scholarly. One should pause to think of the debt which modern medicine owes to Dr. Simon, and to mourn the loss of his charming and inspiring presence.

I shall try to discuss, within the hour, the work on the bacteriology of influenza which has been done during the past few years, and consider the subject in the light of more recent experience. In the interest of a continuous presentation, it is desirable to restate briefly the results of earlier experiments.

EARLIER OBSERVATIONS

In face of the severe pandemic of influenza of 1918, doubt was cast on the significance of Pfeiffer's bacillus as the causal agent of the disease. Competent bacteriologists failed to find the microörganism in the blood or nasopharyngeal secretions of early cases with any degree of regularity, although this organism, as well as other ordinary bacteria, could frequently be recovered from the lungs of persons who had succumbed to a secondary pneumonia. Moreover, it was often found as a secondary invader in other unrelated diseases, such as tuberculosis, whooping cough, and measles; in respiratory infections other than influenza, and in normal persons during interepidemic and epidemic periods. Antibodies against the bacillus could be demonstrated only irregularly in recovered patients and serological tests revealed many distinct types in the majority of cases, although the rapid spread of the epidemic might lead one to suspect the incitant to be of one type. Furthermore, no clearcut evidence was adduced to show that the bacillus was specifically pathogenic for laboratory animals, and finally, inoculations with vaccines did not appear to be generally effective in diminishing the incidence of the disease.

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[1] De Lamar Lecture delivered before the Johns Hopkins University School of Hygiene and Public Health, February 18, 1930.

The unparalleled spread of the 1918 pandemic and the confusion that existed in respect to the causal agent of influenza led a number of investigators to turn to the study of its etiology. While Dr. Gates and I were at work upon this problem, several articles appeared which reported the successful transmission of the symptom-complex of influenza from man to man and from man to monkey by the use of filtered material. Among the many reports were, notably, those of Dujarric de la Rivière (2), Nicolle and Lebailly (3), Yamanouchi, Sakakami and Iwashima (4), and Bradford, Bashford and Wilson (5).

The experiments made by Dr. Gates and myself concerned chiefly the cultivation by special methods of the filtered nasopharyngeal washings obtained from early cases of epidemic influenza. As a ground-work for the cultivation tests, animal transmission experiments were first done with the object of inducing an infection of an influenzal character. The three outstanding characteristics of the human disease which could be used as criteria for interpreting successful animal transmission experiments were considered to be (*a*) the leucopenia, (*b*) the diminished resistance of the lungs which permitted invasion of different bacteria and so opened the way to pneumonia, and (*c*) the pathological changes chiefly edema, emphysema and hemorrhage found inthe lungs of those who succumbed.

The first attempts at transmission of the infection from man to rabbits were made with the unfiltered saline solution washings of the nasopharynx of patients in the early hours of uncomplicated, epidemic influenza. It was expected that the different bacteria ordinarily found in the washings might be suppressed by animal passage and that the specific effects of an extraordinary microörganism might thereby be revealed. Later, filtrates of similar washings through Berkefeld "V" candles were employed. Intratracheal inoculations in rabbits of the unfiltered or filtered material were followed, one or two days later, by characteristic effects (6, 7). They comprised mainly a mild and transitory febrile reaction accompanied by leucopenia which endured for a few days, and from which the animal wholly recovered unless bacteria such as reside ordinarily in the nasopharynx were also injected into the lungs. While such bacteria by themselves do not, as a rule, produce lesions under these conditions of experiment, they were able to multiply in lungs affected by the injection of influenzal washings, and cause severe, and often fatal, pneumonias. On the other hand, when a rabbit was killed at the height of the mild and transitory uncomplicated reaction, the lungs often revealed an inflammation characterized chiefly by edema, emphysema and hemorrhage, but free from the fibrinous and cellular consolidation which is characteristic of pneumonia of bacterial origin.

During the first animal transmission experiments, cultivation tests were made with the filtered nasopharyngeal washings from patients early in the disease and with fragments of lungs, and filtrates thereof, obtained from rabbits injected with influenzal secretions (8, 9).

The special methods used for cultivation of the influenzal material comprised the Smith-Noguchi medium, which consisted of sterile, human ascitic fluid, to which was added a small fragment of fresh, sterile rabbit's kidney, all under a petrolatum seal. Later, there were added collodion sacs prepared in a particular manner (10). The Smith-Noguchi medium was enclosed in the collodion sac, surrounded by distilled water or physiological salt solution. The addition of petrolatum seals established anaerobic conditions throughout the system, and the nutritive and growth-promoting substances of the medium diffused through the collodion in sufficient quantities to support a luxuriant growth in the surrounding liquid. The confusing protein precipitate which formed around the tissue of the medium was confined in the sac. Rabbit blood agar plates incubated anaerobically offered still another means for cultivation, and finally, broth prepared with cultures of *Bacterium coli* (11). In the case of the latter medium, the coli organisms were grown in broth under a petrolatum seal until the bacterial cloud was barely visible. Then the bacteria were killed by heat. The resultant products of *Bacterium coli* served to supply growth-promoting factors and thus enriched the medium. The Smith-Noguchi medium and the blood agar plates were used for primary isolations of microörganisms from filtered influenzal secretions or rabbit lungs; the sacs, for separation of protein precipitate from minute filter-passing organisms so as to permit their demonstration more clearly especially in sparse growths. The coli broth was employed for the preparation of antigen for serological tests. In the course of time, the technique as outlined for isolation of filter-passing microörganisms was changed only in one respect, namely, a different fluid was used for suspending the nasopharyngeal secretions. In the earliest experiments, physiological salt solution was employed; later, dextrose Ringer's solution, and finally, broth. That broth favors the filtration of bacteriophage was first demonstrated by Bronfenbrenner (12), and that it acts similarly in the case of filter-passing anaerobes of the nasopharynx was shown by Mills, Shibley and Dochez (13).

There was isolated from the filtered nasopharyngeal secretions of patients in the early hours of influenza, and from the lungs of rabbits intratracheally inoculated with these secretions, a hitherto undescribed organism, called *Bacterium* (later, *Dialister*) *pneumosintes*. This bacterium was recovered from similar sources during the pandemic of 1918–1919 (8) and during the recurrent waves of epidemic influenza in 1920 (8), 1922 (9), 1923 (14), and 1926 (15). Mention should be made of the fact that during inter-epidemic or epidemic periods the microörganism was not found in cultures of nasopharyngeal secretions of apparently healthy persons, or of patients suffering from non-influenzal affections. Nor was it found in the lungs of normal rabbits or those inoculated intratracheally with non-influenzal material.

At this point, attention should be called to the fact that *Bacterium pneumosintes* has not been cultivated from a large series of patients with common colds. Mills, Shibley and Dochez (13) have obtained similar results. They have made every effort to cultivate the organism except the use of animal transmission and have failed to recover it in their extensive work with normals and with common colds. It appears, therefore, that up to the present the microörganism has been found only in association with true epidemic influenza.

As originally isolated, *Bacterium pneumosintes* was a minute body, of regular and bacilloid form, with its length measuring from 0.15 to 0.3

micron (150 to 300 millimicrons), about 2 to 3 times its breadth. It was capable of passing Berkefeld "V" filters and of resisting the action of 50 per cent glycerol for months. It multiplied slowly and then only under strictly anaerobic conditions. The microörganism was consistently Gram-negative and could be stained, but not deeply, with the usual basic dyes. It formed on the surface of blood agar plates minute, round, convex, amorphous colonies having a colorless or grayish translucence. In media other than the Smith-Noguchi, somewhat longer forms of the organism have been noted but these have reverted to the original minute forms on transfer to the Smith-Noguchi medium.

Later observations have shown that the characteristics just described remain constant over a period of many years—in one case 11 years—when the microörganisms are maintained in the original Smith-Noguchi medium. Furthermore, in this medium the strains require transfer only at long intervals, that is, from six months to a year, since it was found that the organisms remain viable therein at least three years without subplantation.

In early cultures, the *Bacterium pneumosintes* induced in rabbits the characteristic clinical and pathological effects which followed intratracheal injection of the nasopharyngeal secretions of influenza patients and which have already been described. But this pathogenicity was lost during artificial cultivation. However, the more recent experience of Boëz (16) may be of interest in this connection. Old cultures of *Bacterium pneumosintes* were injected intracerebrally in rabbits. They were killed 48 hours later during a febrile reaction. The microörganisms were recovered only from the lungs, and then in pure culture. The other internal organs were negative.

On the other hand, rabbits immunized with *Bacterium pneumosintes* cultures developed specific agglutinins, precipitins, bacteriotropins and complement-fixing bodies (17). A significant feature of the serological tests is the fact that all the strains tested had similar antigenic properties and reacted identically with the specific antibodies produced by any one of them; in other words, all strains behaved as if derived from a common source. Furthermore, the blood serum of patients who had recovered from clinical influenza agglutinated one or more strains of the microörganism, although the serum obtained during an epidemic period from a group of individuals apparently free from an attack of influenza showed similar agglutinins but in a smaller number of instances (15).

With regard to the relationship of *Bacterium pneumosintes* to the incitant of epidemic influenza, it was stated (1) in 1923 that "it has seemed wiser, ... merely to report the experimental facts, and to defer decision of the precise relation which *Bacterium pneumosintes* bears to epidemic influenza until further experience is obtained." And again, in 1926 (15), "a large accumulation of observational and experimental evidence must be sought wherever available, and pieced together as opportunities permit," in the effort to determine this relationship.

THE PNEUMOSINTES GROUP OF MICROÖRGANISMS

Bacterium pneumosintes is not the only anaerobic, filter-passing, Gram-negative microörganism found in the upper respiratory tract of man. From the nasopharyngeal secretions of patients suffering from various respiratory infections and of normal individuals, a considerable number of different bacteria of this group has been cultivated. Credit is due to Dr. Avery of the Hospital of the Rockefeller Institute for his discovery of the first of the groups (later designated as Group I) by means of cultures of filtered nasopharyngeal secretions on anaerobic blood agar plates. His finding was quickly followed by the isolation of two other groups by Dr. Gates and myself (Groups II and III) (9), and again shortly thereafter of still two others by me (Groups Ia and IIIa). In all, at the present time, the literature records more than 30 supposedly different groups of microörganisms of new species isolated from the upper respiratory tract, of which 6 were cultured at the Rockefeller Institute, and 11 additional ones were isolated by workers trained there (Branham (2) and Levinthal (9)).

It is not to be supposed that the different species of these microorganisms are limited to this number. Others may be found from time to time. Nor has the last word been said about the specificity of each one of the groups. It is likely that in a number of instances there is duplication. However this may be, the number of the different groups of anaerobic, filter-passing organisms isolated from the nasopharynx of man is comparable to that of the aerobic bacteria found in the same region. Further work is necessary to show the significance of each group of bacteria, but for the present they may be tabulated and described briefly as follows:

GROUPS OF GRAM-NEGATIVE, ANAEROBIC BACTERIA FOUND IN FILTERED SECRETIONS FROM THE NASOPHARYNX

Bacterium pneumosintes, already described.

Group I (Olitsky and Gates' classification). Vibrios of variable length, motile, showing sparse granular growths in Smith-Noguchi medium. Colonies are large, heaped in the centers, with flat edges, and non-hemolytic. The organisms are autoagglutinable (9).

Group Ia. Long, bacilloid organisms, non-motile, growing as a diffuse cloud in Smith-Noguchi medium. Colonies are raised, round, and translucent, with flat edges; they exhibit zones of brownish discoloration. Serolgical tests reveal their specificity and distinction from members of the other groups.

Group II. Bacilloid, pleomorphic organisms, non-motile, showing no obvious signs of growth in Smith-Noguchi medium; they merely vegetate therein. Plate colonies are translucent and small, and resemble those of *Bacterium pneumosintes;* they do not change the appearance of the medium. Serological tests reveal their specificity (9).

Group III. Short, vibrio-like, tenuous, monomorphic organisms, motile, vegetating only in Smith-Noguchi medium. Colonies are large, with raised, crater-like centers and flat, irregularly spreading edges; they do not change the appearance of the medium. The organisms are autoagglutinable (9).

Group IIIa. Bacilloid, short, tenuous, delicate organisms, some vibrio-like, faintly stained by the usual dyes, non-motile and growing very feebly in Smith-Noguchi medium. Colonies are small, granular, with slightly peaked centers and edges which are toothed; they do not change the appearance of the medium. Serological tests show their distinction from members of other groups (18).

The next two groups have been recovered by Branham (19) from the filtered nasopharyngeal washings of patients with influenza or common cold. They are as follows:

Group I (Branham's classification). This group has the distinction of retaining Gram's stain. It consists of very minute organisms, indefinite in shape, occurring in clumps, and showing microscopic, round, raised, transparent colonies.

Group II. Gram-negative cocci, in diplo form but occasionally in short chains, showing a granular growth in Smith-Noguchi medium and producing hemolytic, round, smooth, shiny, raised, translucent colonies.

Another microörganism, isolated from the filtered nasopharyngeal secretions derived from influenza patients, and called *Bacillus granuliformis*, has been reported by Pavlović (20). This type has a close morphological resemblance to *Bacterium pneumosintes* and is therefore a Gram-negative, anaerobic, non-motile, bacilloid organism, which is stained with difficulty. As described by Pavlović, it is pathogenic for rabbits, inducing a transitory reaction of fever and, generally, leucopenia. The lungs of affected rabbits show also a hemorrhagic lesion, free from pneumonic consolidation, and the intratracheal inoculation of the microörganism may be followed by secondary pneumonias, if combined in action with other ordinary bacteria. It is of interest to note that 60 per cent of the patients studied, in the 1927 epidemic in Belgrade, yielded agglutinins in their sera against this bacillus. Serological tests, furthermore, revealed that antipneumosintes serum agglutinated, and gave positive complement-fixing reactions with *Bacillus granuliformis*. Pavlović, however, maintains that the latter is distinct from *Bacterium pneumosintes*.

In addition, there are recorded by Garrod (21) and by Williams and her collaborators (22) the incompletely classified groups of anaerobic organisms also cultured from filtered nasopharyngeal secretions of man. Garrod reports 2 types: Type I, minute, anaerobic, filterable, Gram-negative coccus, producing microscopic, transparent colonies which are hemispherical and have clear-cut margins. Type II, short, tenuous, Gram-negative bacilli, sometimes curved, producing microscopic, transparent colonies which are pleomorphic, some being flat, others slightly raised or conical, with either smooth or crenated edges.

The next series of microörganisms to be described comprises groups of Gram-negative, anaerobic bacteria found in the nasopharynx of man, the filterability of which is unknown because reports of this characteristic are lacking. The bacteria are tabulated and briefly described as follows:

GROUPS OF GRAM-NEGATIVE, ANAEROBIC BACTERIA FOUND IN THE NASOPHARYNX OF MAN

The first series are those isolated by Levinthal (23). They include 9 different groups of which

Group I (Levinthal's classification), *Streptrothrix anaerobiontica*, comprises thick, thread-like, also short and long bacilli which grow as a diffuse cloud in Smith-Noguchi medium, producing gas when dextrose is added. Colonies are raised, whitish and mucoid.

Group II. Long, tenuous, thread-like organisms forming raised, whitish colonies which are hemolytic.

Group III. Short, monomorphic rods with polar bodies. Colonies are grayish, large and transparent. (These are called *Pasteurella anaerobiontica.*)

Group IV. Bacilli of marked pleomorphism, like Type III Pfeiffer's bacilli (Levinthal's classification). Colonies are small, flat and colorless.

Group V. Coccobacilli resembling Type I Pfeiffer's bacilli, showing a profuse growth in Smith-Noguchi medium. Colonies are flat, shiny and reddish-gray.

Group VI. Bacilloid, pneumosintes-like organisms producing dew-drop colonies. Serological tests show their distinction from *Bacterium pneumosintes.*

Group VII. Tenuous, short and long bacilli, non-motile, which form small, whitish colonies having brownish centers.

Group VIII. Pleomorphic bacilli, labile to Gram's stain, non-motile, forming small, clear, colorless colonies.

Group IX (*Streptococcus parvulus*). Cocci in short chains which remain alive but do not grow in Smith-Noguchi medium and produce minute, clear, colorless, flat colonies.

In addition there are six groups isolated by Thomson (24).

Group I contains organisms regarded by Thomson as types of *Bacterium pneumosintes.* They were isolated from a severe case of Engadine fever (influenza?). They alter boiled blood agar to a cherry red color, and this is the distinctive difference between the organisms and *Bacterium pneumosintes.*

Group II. Gas-producing diplococci which resemble *Staphylococcus parvulus.*

Group III. Non-gas-producing diplococci, which do not grow in fluid medium, otherwise resembling *Bacterium pneumosintes*. These organisms were isolated from the sputum of an influenza patient.

Group IV. Bacilli with marked pleomorphism which are hemolytic and form flat, round colonies with depressed centers.

Group V. Oval diplococci which do not grow in fluid media. They form grayish-white, somewhat transparent, soft and moist colonies.

Group VI. Bacilli which do not grow well in fluid media, but form grayish-yellow, soft, moist colonies.

Under this classification may be included also the 4 groups of anaerobic cocci and 4 of bacilli isolated by Noble and Brainard (25) from nasopharyngeal secretions:

Coccus I (Noble and Brainard's classification). Cocci labile to Gram's stain, forming delayed hemolytic zones and fermenting dextrose and levulose. These cocci were recovered only from cases of common cold (as were those of the next 3 groups) and resemble the ogransisms previously described by Hall (26).

Coccus II. Cocci, Gram-positive, showing indifferent colonies on blood agar plates.

Coccus III. Gas-producing, Gram-positive cocci which are non-hemolytic and ferment dextrose and levulose.

Coccus IV. The organisms resemble those of Group III but differ from them by fermenting saccharose.

Bacillus II (Noble and Brainard's classification). Gram-negative, slender rods, slightly curved and actively motile, which form minute, delicate and translucent colonies. They were isolated from a healthy subject.

Bacillus III. Gram-negative rods, slightly curved with rounded ends, non-motile and forming coarsely granular colonies with scalloped edges. They were cultured from a case of chronic rhinitis.

Bacillus IV. Long, thread-like, Gram-negative rods, showing granules when stained, and forming indifferent colonies on blood agar plates. They were recovered from a patient with acute rhinitis.

Group of Gram-positive Bacilli. Pleomorphic cocco-bacilli, non-hemolytic, which were isolated from a patient with common cold.

Finally, there may be added 2 organisms, the discovery of which has antedated the work of Dr. Gates and myself. They are:

Bacillus rhinitis of Tunnicliff (27), a Gram-negative, anaerobic, curved or wavy, long rod, actively motile and growing in granular form in Smith-Noguchi medium. The colonies are small, round, and "dull" and later become brown. Tunnicliff believed that she could reproduce "rhinitis" in man by swabbing cultures intranasally. The source of this organism is the nasal mucus from patients suffering from acute coryza.

The second is the *Staphylococcus parvulus*, a gas-producing coccus, first isolated in 1898 by Veillon and Zuber (28), and subsequently found in the mouths of man and animals by Lewkowicz (29), who named it *Micrococcus gazogenes alcalescens anaerobius*. A type of this organism which is hemolytic but produces no gas in Smith-Noguchi medium has been described by Branham (30). Noble and Brainard (25) and others have found this coccus so frequently that it is generally regarded as part of the normal flora of the nasopharynx.

It is an impossible task to make a complete list of anaerobic organisms, obtained mainly from filtered nasopharyngeal secretions because investigations are being carried on at the present time, notably by Long at the Johns Hopkins Hospital, and the results are consequently indefinite. Yet the tabulation made above should suffice as a basis for further work until the future demonstrates the significance of each group of these bacteria. It may be said now that in upper respiratory infections, the organisms appear to increase in number, as is shown by our experiments and those of Branham (19) and Long (data not as yet published). In this connection it is desirable to report the results of cultivation experiments made by Long and myself on naso-pharyngeal secretions derived from patients with the upper respiratory infections prevailing in epidemic form in 1928–1929.

RESULTS OF CULTURES IN THE 1928–1929 EPIDEMIC OF UPPER RESPIRATORY INFECTIONS

During this epidemic of an upper respiratory infection—a disease which some have considered as obscure but not influenza (31)—we have found difficulty in selection of cases when the standard for comparison was the characteristic picture of 1918–1920 patients. Of the cases called to our attention, many were obviously non-influenzal, as for example, common colds, sinusitis, pharyngitis, etc., but several were selected for study in which the symptoms were more characteristic of epidemic influenza. There were in all 15 of this kind. In 7 of the 15, the final diagnosis was uncertain in 4 cases; epidemic pneumonia in 2; and pharyngitis in the remaining one. In each of the 7 in which the diagnosis was not definitely influenza, leucopenia was absent: the white blood cell counts varied from over 8,000 to 14,000. Special anaerobic cultures, as described above, of the filtered nasopharyngeal secretions revealed no growth in 2, and of the pneumosintes group of organisms, Groups I, Ia, II (Olitsky and Gates' classification), and *Staphylococcus parvulus* in the others.

The remaining 8 patients showed normal or low white cell counts, in spite of febrile reactions and a symptom-complex which resembled that of epidemic influenza. The disease, however, was mild. None of these patients developed secondary pneumonia; all recovered promptly. Anaerobic cultures of the filtered nasopharyngeal secretions showed the predominant and prevailing organism to be of the Group IIIa of pneumosintes-like bacteria. Seven patients yielded this type. The microörganisms next in frequency of occurrence and appearing concurrently with IIIa bacteria, were those of Group I in 5 cases; II in 4 cases, and Ia in 2 instances.

It is to be noted, therefore, that in certain epidemics of acute infections of the upper respiratory tract, one of the group of pneumosintes-like organisms may be the predominant and prevailing bacterium to be found in the filtered nasopharyngeal secretions.

Dr. Long and I were engaged in the cultivation experiments just described during the period from October, 1928 to March, 1929. Dochez, Shibley and Mills (32) investigated a type of acute infection of the upper respirator tract of man, usually designated by the term "Common Cold," cases of which were occurring at about this time. With the filtered washings derived from patients suffering from this type of infection, Dochez and his coworkers could communicate to apes experimental common colds which resembled closely the human disease. Furthermore, no such reactions were obtained with the secretions from healthy persons, free from upper respiratory infections. From the filtrates in all positive experiments, the investigators have been able to cultivate a Gram-negative anaerobe of Group I of pneumosintes-like organisms. On the other hand, they have cultivated another type of the "group" microörganisms from 6 of 8 filtrates derived from the nasopharyngeal secretions of healthy persons. These results, to which reference will be made again later, also indicate that one type may prevail in filtered secretions, and, as has already been shown (33), that certain "group" organisms may be found in health. In general, the results of Dochez and his coworkers agree with the prior conclusions of Dr. McCartney and myself obtained from inoculation experiments in man (33).

The bacteriological observations recently reported by Falk and his coworkers (34) and based on cases of upper respiratory infections occurring during the epidemic of 1928–1929 have revived interest in the etiological significance of green-producing streptococci. The cocci have been previously implicated as the incitant of influenza by Mathers (35) in 1917, by Tunnicliff (36) in 1918, by Rosenow (37) in 1919, and by Thomson (38) in 1929, but as yet these prior investigations have not been generally accepted as pointing to a solution of the problem. On the other hand, Falk believes that he has added evidence in support of the etiological rôle played by the streptococci. The evidence consists mainly of the recovery of 2 groups of serologically dissimilar cocci—one pleomorphic and the other monomorphic—obtained from influenza material, which produce pathogenic effects in lower monekys and in man, a specific toxin, and specific agglutinin response against them on the part of recovered patients.

THE PRESENT STATE OF THE PROBLEM OF ETIOLOGY

Although considerable effort has been expended on the study of the identification of the causal agent of epidemic influenza, the present time finds the problem still unsolved. There are several factors which contribute to the existing confusion, and the outstanding difficulty arises from the necessity of selecting cases of undoubted acute influenza. There has been in the past frequent failure to recognize influenza as a specific, primary disease, and therefore to consider the various bacterial pneumonias that develop in lungs injured by the influenzal agent as secondary infections. Moreover, the primary, uncomplicated disease is usually mild and transitory; so that unless the incitant is sought in the early hours, it may become masked, or even supplanted by associated organisms. Furthermore, in view of the rapid and extensive spread of influenza during pandemics, it becomes difficult to select for control observations, cases of perfectly healthy individuals who have never suffered from the disease. Finally, to add to the confusion, a clear clinical distinction has not always been made between primary, uncomplicated, epidemic influenza and many different types of upper respiratory infections, such as common colds, acute rhinitis, acute bronchitis, and other indefinite conditions, which may simulate a true influenzal attack.

Hence there are three different agents for consideration and for future study of their precise relation to the cause of epidemic influenza: (*a*) Pfeiffer's bacillus, or other ordinary bacteria which are normally inhabitants of the upper respiratory tract; (*b*) a true filterable or ultramicroscopic virus, and (*c*) *Bacterium pneumosintes* or the group of pneumosintes-like organisms.

In the case of Pfeiffer's bacillus, the opinion is widespread that it plays the rôle of a secondary invader for the reasons which have already been mentioned. Yet there are still a number of investigators who believe that it is the sole exciting cause of primary influenza. The more or less ubiquitous occurrence of the bacillus need not necessarily indicate that it is not the incitant of the disease, for some investigators hold that from time to time its invasiveness and virulence increase to the point at which the organism becomes capable of inducing epidemics (39). Furthermore, many types of the bacillus have been discovered (40) since the original work of Pfeiffer, whose investigations opened up for study the vast field of hemophilic bacteria. It is thought by some that only a special type of Pfeiffer's bacillus is involved in the causation and wide dissemination of influenza, and failure to realize this has led to confusion in interpreting experimental results. Others believe that symbiosis with other organisms, such as streptococci or the individuals of the aerobic flora of the oro-nasopharynx, is necessary for the growth and increase in virulence of Pfeiffer's bacilli (41). An important contribution to the subject of specific pathogenicity of Pfeiffer's bacilli was made by Blake and Cecil in 1920 (42). They employed a culture ultimately derived from a case of influenzal pneumonia, which had lost its virulence by prolonged artificial cultivation. Its virulence was restored by 11 successive passages in the mouse followed by 13 successive intraperitoneal passages in the monkey. Nasal inoculation of monkeys with the altered culture induced an infection which Blake and Cecil regarded as essentially identical with influenza with respect to its clinical course, symptoms, and complications. Later, intratracheal inoculations of 10 monkeys with this organism induced in 7 a hemorrhagic bronchopneumonia similar to the spontaneous pneumonia ascribed to the action of Pfeiffer's bacilli. The investigators infer, but do not definitely conclude, from the experimental results that the bacillus is the cause of influenza. But Jordan (39) explains the results by regarding the organism as a common secondary invader, inducing its characteristic effects which, in turn, obscure those of the primary incitant. Additional study is, however, necessary to show whether or not this, and the other beliefs mentioned are valid.

There are still others who assert that should the incitant of influenza prove eventually to be filterable, then Pfeiffer's bacillus need not necessarily be excluded from playing the rôle of causal agent, since it, also, is filterable. Pfeiffer, Prausnitz, Happe, and Dujarric de la Rivière (43) have shown experimentally that either granules in association with the bacillus, or the microörganism itself, might traverse the walls of the more porous Berkefeld and Chamberland filters (L1 and L2). Recent studies have proved that a distinction should be made between organisms which may traverse the more porous filters in numbers sufficient only to inoculate the filtrate and those which reach the filtrate in almost undiminished concentration (Mudd (44)). For example, Bronfenbrenner and Muckenfuss have reported (45) that instead of representing a filterable stage in the life cycle of the bacteria which sometimes yield growths in filtrates, the secondary growths are the results of imperfection of the filter itself, or of faulty technique. Grinnell (46) has summarized his views on the subject as follows: " . . . . the reported filtration of such organisms as streptococci, bacilli of the enteric group, diphtheroid bacilli and tubercle bacilli might be due rather to the passage of fragments of the bacteria in old cultures still capable of reproduction or to filtration in a particularly favorable suspension fluid than to the existence of a filterable stage in the life cycle of the organism." Hence in respect to its irregular filterability, Pfeiffer's bacillus appears to be no exception to the rule governing ordinary bacteria. In this connection the pneumosintes-like organisms are of a different order. They are ordinarily obtained from filtrates of nasopharyngeal secretions which are, as shown by cultivation tests, free from familiar bacteria, including, as a rule, Pfeiffer's bacilli. Mudd (44) believes that minute size or motility, characteristic of many of the pneumonsintes-like organisms, is one of the important factors in effecting filtration.

Considerable attention has recently been given to the etiological significance of other ordinary bacteria of the aerobic flora normally inhabiting the upper respiratory tract. Of particular interest is the green-producing streptococcus. The fact that this organism ordinarily leads a saprophytic existence in the upper respiratory tract, that it is widespread in occurrence without approved relationship to health or disease, and that it is so ubiquitous as to make its recovery even from the air a relatively simple matter (Olitsky and Long (47, 48)), would indicate that its real significance as the incitant is questionable. But here again the problem may eventually resolve itself, as in the case of Pfeiffer's bacillus, in the implication of a particular, specific, pathogenic type. Since work on this subject is still in progress, judgment should be suspended until further proof is adduced.

With respect to the second class of possible incitants of epidemic influenza, namely, filterable or ultramicroscopic viruses, as distinct from cultivable, filter-passing microörganisms, it may be said that practically all of the experiments (2–5, 49–54) dealt with the transfer of the infection from man to man or from man to monkeys by means of filtered secretions. Although the transmission experiments in these instances were successful, cultivation tests either were not done or were made in a desultory manner so that it is not clear at the present time whether the particular experimental findings support the belief either of a filter-passing bacterium or of a true, non-cultivable, ultramicroscopic virus as the respective incitants. It is therefore apparent that here again additional experimental evidence is necessary before a conclusion may be reached.

The third class of possible incitants of epidemic influenza comprise the pneumosintes type of filter-passing microörganisms. Dr. Gates and I still maintain our cautious attitude in respect to the precise relationship of these microörganisms to epidemic influenza. Those who realize the difficulties of the problem will support this viewpoint.

To be sure, it may be said in favor of *Bacterium pneumosintes* that it has been recovered thus far only from influenzal material. Apart from our findings, the organism has been obtained by Loewe and Zeman (55), in New York, from the filtered nasopharyngeal secretions of influenzal patients, and has produced a characteristic clinical and pathological picture when injected into experimental animals (56). Gordon (57), in London, also reported evidence of the same bacterium in 14 of 20 influenza patients, and in 2 of 3 fatal cases. Lister (58), in South Africa, obtained 5 cultures of an identical anaerobe in 11 patients within 24 hours of the onset of epidemic influenza. He reported 4 febrile reactions, 1 fever and leucopenia, and 1 case of typical influenza among 12 volunteers sprayed with unheated cultures, and no reactions among 6 volunteers sprayed with heated cultures. In addition, Nakajima (59), in Tokio, cultivated 2 strains from pharyngeal secretions and 1 from the lungs of a fatal case of influenza. In the same year, Seitz (60), in Zurich, observed masses of minute bodies in the respiratory exudates of influenza patients and grew them for a time in mixed sputum cultures. Detweiler and Hodge (61) obtained 3 strains morphologically similar to *Bacterium pneumosintes* from filtered influenza material, 2 from lung filtrates and 1 from filtered nasopharyngeal secretions. Subcultures failed to grow, so that identification was not completed. The work of Thomson and the 3 strains which he has isolated from influenza cases have already been mentioned (24). In 1926, Hall (62) cultivated a strain of pneumosintes from the lungs of an animal experimentally infected with the secretions from a patient with typical epidemic influenza. Branham (19) reported the isolation of 4 cultures of either Group II or *Bacterium pneumosintes* from 3 patients with influenza and from an apparently healthy subject. These failed to grow after the first to seventh subculture, so that differentiation could not be completed. The cultivation experiments of Pavlović have already been mentioned (20). Finally, in 1929, Donadei (63) recovered from the nasopharyngeal secretions of a patient with influenza a pneumosintes-like organism which, before discernible cultivation in Smith-Noguchi medium could be obtained, had to be passed through the lungs of 5 successive rabbits.

In view of the uncertainty in identifying the different bacteria of the pneumosintes group, the question arises whether the microörganisms reported by the investigators just mentioned have been definitely classified. This difficulty, and the discrepancy in the results of others who failed to cultivate any organisms of this type, show that the mode of procedure and the cultivation technique require further development and simplification.[2] After a simpler procedure and a more satisfactory medium have been devised, the problem of the exact relation of the pneumosintes organisms to the causal factor of epidemic influenza may be solved.

COMMON COLD AND EPIDEMIC INFLUENZA

Before closing the subject, a brief consideration will be given to the relationship of common cold to epidemic influenza.

There has developed an opinion among several investigators, exemplified notably by Townsend (41), that an intimate correlation exists between the common cold and epidemic influenza. "Although we speak of influenza and the common cold (epidemic coryzas or catarrh, which may be taken to mean one and the same thing) as separate entities, it seems to be impossible for investigators who study the epidemiology of both conditions to separate conclusively influenza from the minor respiratory disorders, of which the common cold is a notorious example" (Townsend).

On the other hand, as Jordan (39) points out, epidemics of colds are related to weather and seasonal conditions, while pandemics of influenza are not notably so. Furthermore, the spread of colds is more limited in area and the rate of dissemination is slower; the age-specific mortality rates are different; the mortality from pneumonia and from abortion is specifically high in influenza. Finally, recovery from common colds does not leave a person resistant to a closely following attack of influenza (64).

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[2] In this connection it may be of interest to give the results of a recent experience. Old Smith-Noguchi cultures of influenzal material, taken in 1926, (15) and at that time set aside as negative, were recently (September, 1929) re-examined. A series of tubes from a common source, namely, filtered lung tissue from a rabbit inoculated with influenzal secretions, showed typical, identified, and now actively growing *B. pneumosintes*. In other words, the original cultures were too uncertain for identification, and furthermore, the pneumosintes organisms therein survived without transplantation for a period of at least 3 years. Also, an additional strain, missed in 1923, and freed ultimately from contamination over a period of 5 years, is now in stock. The 1923 report (14) should therefore read 5, instead of 4, pneumosintes cultures isolated—the added culture being derived directly from the secretions of an influenza patient.

A sharp clinical distinction can also be drawn between cases of true epidemic influenza and common colds. It is not necessary to describe the symptom-complexes here, since this has already been done in a comprehensive way by Jordan (39) and others. Attention, however, may be focussed on the well-known, and measurable, sign in influenza, namely, the leucopenia and especially, in the early hours, the depression in mononuclear cells (65). This condition is absent in common colds, in which the white blood cell count may be normal, or higher than normal with a tendency to an increase in polymorphonuclear cells.

While the distinction between the two affections as they occur during pandemics or epidemics is sufficiently marked to permit definite diagnoses, no such characteristic differences may be revealed between severe common cold and mild influenza during inter-pandemic or inter-epidemic periods. It is such cases which add to the difficulty of the problem, as has already been pointed out. "But to identify as influenza all the sporadic cases, localized epidemics, and weather-conditioned outbreaks of clinically similar disease in inter-pandemic periods hardly seems justified" (Jordan (39)).

A wide variety of different incitants has been implicated as causal agents of the common cold (39, 41). The reports of Kruse (66) and of Foster (67) are of interest; these investigators have been able to produce colds in man experimentally with the filtered nasal secretions obtained from patients having the disease in an acute form. McCartney and I (33) have also obtained similar results in experiments in man and we have shown furthermore that while organisms of the pneumosintes group could be isolated from the spontaneous and the experimental disease, no one type could be, as far as our limited experience has shown, implicated as the causative factor. As mentioned earlier in this paper, however, one type of these microöganisms could be found prevalent and predominant in a group of patients studied at the same time. The results of the recent work of Dochez, Shibley and Mills (32) on anthropoids, already mentioned, are in accord with our findings on the transmissibility of common colds by filtered nasopharyngeal secretions and on the relation of the anaerobic, filter-passing flora to the natural and the experimental disease in man.

The inference which may therefore be drawn from the experiments with filtered secretions is that one type of upper respiratory infection, usually designated as common cold, may be caused by a filterable agent. Whether the agent is a true ultramicroscopic virus, or one of the filter-passing bacteria, remains to be determined.[3]

CONCLUSIONS

One may conclude from what has been stated in the preceding paragraphs that the question of the precise agent causing epidemic influenza cannot be, at the present time, definitely answered (68, 69).

The confusion which now exists may be ascribed to a number of factors. One obstacle to overcome is the difficulty of distinguishing between the primary, uncomplicated infection and the secondary pneumonias which develop in lungs previously injured by the true etiological agent; the lungs in such instances show the marked differences in histopathology resulting from the invasion of a wide variety of microörganisms. It should be mentioned that the different bacteria of ordinary species found associated with influenzal pneumonias are those which several investigators have at one time or another regarded as the primary cause of influenza. As compiled by Jordan (39), they comprise the *Bacillus pfeifferi*, pneumococci, green-producing or hemolytic streptococci, staphylococci, *Micrococcus catarrhalis*, members of the Pasteurella group, Friedländer's bacillus, and finally, combinations of two or more organisms of the ordinary species (the so-called composite, or symbiotic infections).

Another difficulty lies in the selection for study of a patient in the early hours of infection: the disease is transitory, the acute stage enduring for only a few days. As a rule, the patient comes to the attention of the bacteriologist when secondary invasion by ordinary bacteria has set in, which complicates, and perhaps suppresses, the primary incitant. Furthermore, epidemics occur explosively with the result that many cases may be offered for examination at about the same time and each cannot be studied in the most desirable way. Still another hindrance arises from perplexity in selecting, during widely spreading epidemics, individuals for control observation, that is, those who have not been attacked by the disease. Again, in respect to the subject of filter-passing anaerobes of the human nasopharynx, lack of a more simple, uniform and exact technique in collecting and cultivating material, and the absence of a precise taxonomy, are troublesome factors. Finally, experiments such as are made upon laboratory animals, including the lower monkeys, are hedged by impediments. Influenza is not known to occur naturally among them; hence the question arises when an experimental infection is induced as to whether it is or is not true influenza in the particular species involved. Many of these animals when taken from stock suffer from snuffles (70), as is the case with rabbits, or from this or obscure respiratory infections in the case of other animals.

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[3] The recent studies of van Loghem (van Loghem, J. J., An epidemiological contribution to the knowledge of the respiratory diseases, J. Hyg., 1928–1929, xxviii, 33) should be consulted for his hypothesis. He regards common colds as non-contagious, commensal infections induced by changes in air temperature; influenza, however, is contagious and follows its own epidemic course.

On the other hand, a survey of the recent work done on the subject of the incitant of epidemic influenza shows that in spite of all the difficulties which have been mentioned, considerable progress has been made. At the same time, the importance of influenza and related respiratory infections upon the communal well-being has been recognized with the result that the problem is receiving more attention by investigators than ever before.

The advances made in this field relate to sharper definitions in the clinical and pathological pictures of influenza and other upper respiratory infections and to the valuable epidemiological data of these affections. Furthermore, the large and important group of hemophilic bacteria, several members of which are definitely disease-producing, has been discovered, and the group of anaerobic filter-passing bacteria of the nasopharynx of man has been brought into light for examination for the first time. In addition, serious study is being given not only to the significance of each of the anaerobic and aerobic bacteria comprising the flora of the upper respiratory tract in influenza and related infections, but also to the problem of what constitutes the ordinary bacterial inhabitants of the naso-oropharynx in health. Finally, with regard to the selection of an animal suitable for transmission experiments, the recent work of Dochez and his colleagues has shown that the employment of anthropoids offers advantages which ordinary laboratory animals do not possess. It is hoped, therefore, that investigations in which apes are used as the animals of choice will make considerable progress toward the solution of the problem.

In the end, the expectation is that all obstacles will be eventually overcome and this in turn will lead to the goal of an exact knowledge of the etiological agent of epidemic influenza.

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PNEUMONOCONIOSIS AND TUBERCULOSIS

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I. HISTORICAL RESUMÉ OF PNEUMONOCONIOSIS

Occidental civilization has passed slowly and tediously from a predominantly pastoral and agricultural to a predominantly industrial alignment. In the course of this transition many of our modes of living, much in our habits and in our methods of dress and much in our individual and collective point of view has changed. Numerous physical strains and stresses have been lost and new ones have been acquired. The general character of a good many diseases has changed in this shift toward industrialism and new diseases have evolved. Few of all these have been more devastating to health and life than those associated with the breathing of dust.

Our knowledge of the presence of pneumonoconiosis in historic times is meager and will doubtless remain so. But Collis (34) has given an admirable, brief statement of that knowledge, from which we may deduce the belief that the starting point of man's progress was associated with at least some pneumonoconiosis. He has shown that (35) the flint-knappers of Brandon, "the lineal occupational representatives of this the oldest of industries, who still use tools similar in shape to the deer-horn picks of their prehistoric ancestors, suffer a terrible mortality from phthisis induced by flint dust generated in their work."

Although the significance of "industrial" diseases has been greatly augmented in the last three-quarters of a century, these diseases have been more or less recognized since the pre-Christian era. In earlier times the extent to which the general population was affected by dust was limited, and the "dusty trades" concerned but few except miners and stone masons, until the end of the eighteenth century. Yet the menace was noted at least as early as 76 A.D. for in that year Pliny (157) wrote that "Those employed in the works preparing vermillion cover their faces with a bladder-skin, that they may not inhale the pernicious powder, yet they can see through the skin."

It is perhaps not generally known that by the middle of the sixteenth century mining had become an important industry in several parts of the world and that in the year 1556 Agricola (1) published (posthumously) an excellent treatise which covered many different aspects of mining, including the diseases and ills to which the miners are often heir. In 1912 this work was translated into scholarly English by Herbert C. and Lou Henry Hoover (93).[1] Agricola pointed out the danger experienced by miners from dust which "penetrates into the windpipe and lungs, and produces difficulty in breathing . . . . it eats away the lungs and implants consumption in the body; hence in the mines of the Carpathian Mountains women are found who have married seven husbands, all of whom this terrible consumption has carried off to a premature death."

That "consumption,"[2] so-called, was a frequent concomitant of the pulmonary diseases common to workers in dust and often confused with the latter, is clear from the literature; aside from the statement of Agricola just quoted, there is good collateral evidence that even at this time—the middle of the sixteenth century—it was recognized that the inhalation of dust not only led directly to serious intrinsic disease but that it distinctly predisposed to consumption, which term, although obviously used loosely, must have meant tuberculosis in a large number of instances. Paracelsus (152) in 1567 described consumption among miners. One hundred years after Agricola, Borelli (19) stated that the smoke from candles was a common cause of consumption in studious persons. Ramazzini (165) in 1705 described diseases of stone cutters by saying that workmen "oftentimes suck in, by Inspiration, the sharp, rough, and cornered small Splinters or Particles which fly off; so that they are usually troubled with Cough, and some of them turn Asthmatic and Consumptive." The prevalence of phthisis or consumption was noted among quarrymen by Coschwitz (40) (1721); among stone cutters in 1727 by Wepler (226); among marble workers, needle grinders, etc., by Simmons (192), Desgenettes (47); and Johnstone (97) before 1800.

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[1] This translation is beautifully done and is richly embellished with useful, explanatory footnotes. It is bound in facsimile, the old wood cuts are reproduced, and altogether the translation makes up into a most attractive and valuable source book. It adds to the interest in the volume that the translators now live in the White House.

[2] Critique of terminology, of errors of diagnosis, etc., is considered in the section entitled "Relationship between Pneumonoconiosis and Tuberculosis."

The dusty trades had increased sufficiently in number and importance by the year 1705 to cause Ramazzini to write the first book on occupational diseases. As industrialization has increased there has developed quite a voluminous literature which concerns itself both with the diseases that follow as a direct consequence of the inhaled dust and also with the infectious diseases commonly associated with the latter.

One of the signs very commonly associated with pigmentation of the lungs, especially of workers in coal, is the discoloration of the sputum, known for a long time as *black spit* and thought to be a disease entity. Black spit (as an entity) has called forth a great deal of writing. Thomas Willis (232) alluded several times to it. He contended that it was of no great significance in itself but that it was frequently a forerunner of purulent sputum. This is an astute observation and may represent the fact that tuberculosis with its purulent sputum was at that time a common (though late) complication of pneumonoconiosis. Morton (138) in 1689 thought it prognostic of consumption and in 1780 Portal (160) described three varieties: (1) that depending upon inhalation; (2) that secreted by the bronchial glands and (3) that derived from extravasated blood. According to him it may be present for years in perfectly normal people.

The origin and significance of pigmentation of the lungs was thus at one time a subject of much discussion and misunderstanding. As just indicated its origin was attributed by some to a secretion, by others to deposition of blood pigment and by still others to inhalation. The common belief that the black matter in the lung was secreted by the tracheobronchial lymph nodes was held by Morton and concurred in by many subsequent writers (Senac (188), Withers (235) and others). Bree (20) referred to it as the carbon of the blood. Morgagni (137) saw black lumps in the tracheobronchial nodes in 1761 as also did Mascagni (125) a little later. Henry (83) chemically examined fluid from a melanotic mass and found that it corresponded to the natural black pigments and not to carbon. He apparently analyzed a mass of melanotic tumor. Becker (13) contended in 1826 that the chief function of respiration is to decarbonize the blood. If the blood contains more carbon than the oxygen of the air can convert into carbon dioxide, the excess carbon may conceivably be precipitated into the lungs to form the black matter (see Thomson (206)). In 1808 Soemmering (196) stated that the inhaled particles "from the burning of bad tallow or coarse oil" could reach the tracheobronchial nodes only through the air passages. Pearson (154) in 1813 extracted a black powder from the lungs and tracheobronchial nodes of human beings and established its identity in every case with that of charcoal. The charcoal was deposited in an orderly arrangement which corresponded to the arrangement of the pulmonary lymphatics depicted in Cruikshank's (46) drawings and caused him to state that pigment in the lungs is laid down along the lymphatic vessels. He remarked, "as hath been repeatedly observed, the lungs generally become more dark coloured proportionately to their age;" and he advanced the idea that dust reaches the lungs with the inspired air and is transported *by lymphatics* from the air spaces to the bronchial nodes.[3] A very few years later Chomel (27) (1817) wrote that sputum streaked with black was commonly observed in those who have been for long in an atmosphere "loaded with the vapours of oil or of tallow." It is interesting that

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[3] Reisseissen (168) in 1808 thought the dust was especially abundant where the lymph vessels collected and that the particles were doubtless within the vessels. See Miller (132).

Laennec explained the presence of pigment in the lungs of adults, which is absent in children, on the basis that the older people sat up more at night and, in doing so, inhaled the fumes and smoke from lamps. He, however, indicated that definite differences existed between melanosis which did not stain the sputum and which should be regarded as "cancer" and the black deposits of carbon in the lung. In this Fawdington (53) concurred in 1826.[4]

The idea was prevalent at Pearson's time and even a good deal later that pulmonary discoloration was present and probably responsible for several separate entities which fell into three main groups and were classified as (1) healthy black matter, (2) true melanosis and (3) spurious melanosis. But Craig (42) declared in 1834 that the inhalation of dust was responsible for all forms of lung-black and that the different items in the classification of "melanosis" represented simply varying amounts of charcoal or carbon that had been breathed into the lung. Graham (68) wrote also in 1834 and, accepting Pearson's work, suggested that inhaled carbon particles from miner's lamps were the cause of the discoloration. He explained the freedom from symptoms of the people with pigmented lungs on the basis of the smallness and therefore the nonirritating properties of the carbon particles.

As the source of the pigment in discolored lungs became more clearly understood, new terms, descriptive of the type of dust were applied. Thus the term *anthracosis* was suggested in 1838 by Stratton (198) to distinguish the condition of impregnation with extraneous dust from the more malignant *melanosis*. Zenker (238) described iron pigment in the lungs and gave the condition the name *siderosis*. He also suggested *pneumonoconiosis* as a generic term to include the condition resulting from the inhalation of dust of any sort. Since that time such terms as *silicosis* (sand), *lithosis* (stonedust in general) *chalicosis* (copper), *calcicosis* (lime, marble) and *asbestosis* among others have been coined for special use. Kuborn (109), who did a great deal of work among Belgian miners, declined to think of "anthracosis" with its *black spit*, etc., as a disease entity (Crocq (43)).

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[4] In the present state of knowledge, it seems a little surprising that the distinction between melanotic sarcoma and pneumonoconiosis should have even been the subject of great dispute and polemic as well as one of considerable misunderstanding. But that it was a very live issue one hundred years ago is clear from the literature.

Although Pearson's demonstration was sharp and clear, numerous continental writers persisted in presenting other sources of origin for the pigmentation, and this in face of the fact that several observers, especially in Scottish coal mines, had adduced much observation and logic in support of the inhalation notion. Of the Scottish writers the clinical observations of Thomson (206) who wrote in 1836 stand out clearly. He differentiated between the effects of inhalation of coal and other dusts and remarked that stone cutters employed in the collieries to cut the rock lying between the seams of coal died much earlier than the coal miners. He stated "Four men . . . . died with black spitting; all of them stone workers. Three brothers and four sisters, of the same family, who have worked in the pit, but not at stone-work, are all well;" and: "Twenty-two persons, all stone-workers, have died of the disease (black spit), while forty-one persons of the same families, who are accustomed to work in the pit (i.e., mining coal), are in good health."[5]

Pearson's position was challenged by several leading pathologists, especially in Germany, who stoutly maintained that the inhalation concept did not represent the truth. As has already been intimated, the belief was held earlier that the bronchial lymph nodes secrete a bluish-black substance which was responsible for their discoloration and, in a way imperfectly understood, responsible also for the discoloration of the lungs. Such a belief was still maintained by some. In 1841 Hasse doubted whether the pigment in the lung, granted to be carbon, was of extraneous origin. Virchow (216) a few years later held that the pigment was derived from haemoglobin. The great anatomist, Henle (82) (1841) on anatomical grounds rather opposed the idea of inhalation of dust since it was difficult to see how inhaled dust could be carried over into the lymphatics from the air spaces.

Two men isolated particulate matter from lungs of miners in 1860. Peacock (153) found in the ash of lungs of buhr stone cutters, insoluble particles which he thought were identical with the stone on which they had been working. Traube (210) at the same time had recovered isolated particles of carbon from a coal miner's black lung. After this, Virchow (217) finally admitted (1866) the possibility both that dust might be inhaled and might cause discoloration of the lung. In the same year Koschlakoff (108) had contended that, because he could find little or no pigment in the alveoli and their walls when it was constantly present in the walls of the larger bronchi, the pigment was formed from within and therefore from the flood. According to Arnold, Pokatilow (158) in 1870 injected or poured blood into the trachea of experimental animals which he then allowed to live for various lengths of time. He found, in addition to the yellow blood pigments, numerous small black specks scattered widely throughout the organ and contended that these latter were of endogenous origin. According to Zenker, Seltmann (187) was among the first Germans to write his own experience as physician to miners. In 1863 he was convinced of the correctness of the "inhalation theory." Rindfleisch (177) described a piece of charcoal in the lung which had retained the normal arrangement of the pores of the wood.

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[5] This is a quotation from a letter sent to Thomson by a fellow-physician at a neighboring mine. Quite a group of Scottish physicians labored to put across the idea of dust inhalation as the source of pigment (and disease) in the lungs. Among them were: Thomson (206), Craig (42), Graham (68), Stratton (198), Marshall (124), Hamilton (78), Alison (3), Carswell (25), Gregory (73).

But even the Virchow admission did not settle the question for all time, for it was again raised in 1905 when Vansteenberghe and Grysez (213) sought to support Calmette's contention. Calmette and Guërin (23), in studying tuberculous infection, had maintained that the digestive tract is the portal of entry for the tubercle bacillus which produces pulmonary tuberculosis. To show that this circuitous route is the normal one for foreign matter in the lung, Vansteenberghe and Grysez fed various dusts to animals and in this manner claimed to have produced lung-pigmentation. They noted the significant fact that the age of the animal (guinea pig) is important in the pigmentation of pulmonary tissue. In their experiments they found the lungs of adult animals pigmented and those of young animals free from pigment and concluded that pigment enters the body by way of the digestive tract; in young guinea pigs this pigment is prevented from reaching the lungs by the relatively impervious mesenteric nodes, whereas, in old pigs, the foreign matter is not so held up for the reason that the mesenteric nodes become permeable with age. They brought forth this idea as an hypothesis, without presenting sufficient evidence to support it. It has been clearly shown (Willis (231)) (1) that pigment slowly and gradually accumulates in the lungs of practically all guinea pigs which are kept in a laboratory for as long as a year, (2) that no pigment is found in the lungs of young guinea pigs, and (3) that in these circumstances pigment shows no tendency to accumulate in the mesenteric nodes in either young or old guinea pigs. The obvious explanation of these observations is that the longer the animals (and man) live, the more often the opportunity occurs for them to breathe particulate matter into the lungs, where most of it remains. As more particles are thus brought to the lungs, the concentration ultimately becomes sufficient to produce a gross pigmentation of the organs. In this connection it is interesting that Lehmann (114) noted that much inhaled dust adheres to the mucous membranes of the nose and throat and is eventually swallowed. He estimated that 90 per cent of inhaled dust is retained and that of all dust taken into the body, 60 per cent is swallowed. The work of Oliver (146) written from extensive clinical and laboratory experience, that of Montgomery (136), and of Findlay (56), each of whom did exhaustive pigment-feeding experiments, seems definitely to establish the air route as the prevailing portal of entry for the dust that produces pulmonary pigmentation. Mace (122) produced additional evidence on this point when he injected talc intraperitoneally into guinea pigs and at intervals up to four weeks autopsied the animals, mashed and completely burned the lungs in a porcelain crucible, and treated the residue with hydrochloric acid. No talc was found.

The question of the effect of pneumonoconiosis upon tuberculosis and of the relationship between the two diseases is an engaging one, the literature upon which roughly shapes itself into three groups. The writers of the first and by far the largest group claim that the changes set up in the lungs by inhaled dust definitely predispose to pulmonary tuberculosis. This is obvious from what already has been said above. In the sixteenth and seventeenth centuries many men noted the prevalence of consumption among quarrymen, miners, marble and plaster workers, grinders, stone-cutters, needle-factory employees, and other workers. Thackrah (202) in 1831 reported finding many young widows in the mining population and presumed that the premature death of their husbands had come about from the nature of their occupation. More recent literature abounds in expression of a similar point of view. Collis (34), Oliver (146), Lanza and Childs (113) Watt, Irvine, Johnson and Steuart (225) Middleton (128), Drury (50), and many others have, from clinical, pathological, and statistical observation, reported that silicosis definitely renders one liable to develop tuberculosis and just as definitely hastens the process toward a fatal issue, once it is developed. Experimentally, this contention has been repeatedly supported. An analysis of the validity of data on which many such claims are based is presented in the section on the Relationship between Tuberculosis and Pneumonoconiosis.

Another group of authors purports to show that miners' phthisis, as such, is not wholly responsible for the high mortality from tuberculosis among workers in dust and that there are numerous contributory and collateral factors which ought to be considered as being of importance. Some of these writers held that general and personal hygiene was of great significance. For instance in 1831 Benoiston de Chateauneuf (16) was emphatic in pointing to postures which embarrassed pulmonary expansion and to the inhalation of impure air (aside from the dust) as such factors. In the same decade Lombard (117) pointed to a lack of proper food, clothing and shelter as contributory to ill health of miners.

Certain other of these writers thought bacterial contamination of the dust was important. As early as 1705 Ramazzini (165) postulated some "unperceivable" element associated with dust as the cause of symptoms of workers. This author may be quoted as follows: "When I consider how strange it is, that so pernicious a Powder should flow from such a benign Grain as Wheat, I am tempted to suspect that this Powder has Worms in it unperceivable to the Senses; and that these Worms being put into Motion, and Dispersed through the Air. . . ." give rise to a multitude of symptoms. Rambousek (166) held that a great danger from dust articles lay in their capacity to carry germs with them when inhaled and remarked that "where no dust is there are no bacteria in the air." Within the year, Augustine (7) has injected into guinea pigs the washings of the air of the sick room of people with tuberculosis,—with equivocal results (one animal out of fifty used in twenty-four experiments developed tuberculosis). She injected washings containing dust from the walls, floor, rugs and furniture, etc. from the sick room (as did Cornet (39) years ago) and produced tuberculosis in one-fourth of the animals. This, however, does not prove that the bacilli were actually carried along by the dust, although such might easily be possible. Landis (110) thought that dust particles might act as vehicles for carrying tubercle bacilli into the body and believed that the general hygienic and economic surroundings of workers in dust are matters of more importance in producing pulmonary disease than is the inhalation of dust *per se*. In the opinion of Watkins-Pitchford (221) tubercle bacilli may be found in a very high percentage of silicotics in the late stages of the disease when necrosis is present but there is often slight or no histological evidence of tuberculous tissue: the bacilli encountered under these circumstances are to be regarded as saprophytes. But he was convinced that histopathological evidence of tuberculosis points to a tuberculous complication of the silicosis, for the silicotic lung in all stages is more liable than the normal to tuberculous infection. This author believed, however, that the general unsanitary conditions in the mines account for a great deal of tuberculosis among the workers. Upon examining 250 specimens of sputum taken at random from the floor of the mines he (222) found that 15.2 per cent contained tubercle bacilli, while only 2.5 per cent of 120 specimens from the surface where workers were employed outside the mines contained bacilli. Lanza and Childs (113) found a great deal of tuberculosis in the very unhygienic surroundings of the homes of the zinc miners they investigated.

A third group of authors attempts to show that certain dusts (mostly coal) actually act as a preventive against the development of pulmonary tuberculosis. As early as 1763 Clapier (29) reported having cured a patient of consumption by causing him to live in a coal mine. Coal dust has been administered therapeutically by inhalation in tuberculosis (Klotz (103)). Beddoes (15) reported the fact (1796) that an inhalation apparatus had been devised but that "whether it will be useful to coat the pulmonary ulcers with fine charcoal . . . . remains to be tried." Vernois (214) noted an exceptionally low death rate from tuberculosis among coal dealers. Hirt (87) explained his observation of but little tuberculosis in coal miners by saying that: "it is in the highest degree probable that coal dust possesses the property of hindering the development of tuberculosis and of arresting the progress." It has been reported (Goldmann (67a), Purdy (163)) that the death rate from tuberculosis was actually lower in coal miners than in their families. Shufflebotham (19) has also commented on the relative rarity of tuberculosis in coal miners and has cited the following mortality rates: for England and Wales for all occupied males, 175; for coal miners only 85. To this there is an occasional dissenting voice. For instance, Crozier (45) reported that the death rate for tuberculosis in the coal miners of Saint Etienne is nearly double that for the entire district. He stated that pathologically among these workmen dust is most concentrated at situations in the lungs where tuberculosis is located, and that coal dust seems to be an important factor in the development of this infection, which, however, is more fibroid and chronic than that in nonpigmented lungs.

No historical consideration of this subject would be in any way complete without an account of the efforts at prevention that have been made. Although this question is presented in the section on prophylaxis, comment should be made at least upon the efficient manner in which this issue has been managed in the mines of South Africa. In 1902 a commission was appointed by the British Government to investigate conditions in that country, especially in respect to "miners' phthisis." It determined that "the disease falls most heavily on rock-drill miners," who died at the average age of 35; that the incidence of the disease was greater in "dry" mines; that clinically there were to be found (1) a pure, nontuberculous type of phthisis; (2) a mixed fibroid type; (3) a tuberculous type and (4) a *very* chronic type with fibrous changes in the lungs and evidences of cardiac and renal disease. A second commission, appointed in 1907, emphasized the desirability of ventilation and the analysis of mine-air, and formulated standards of air-purity. In 1911 The Miners' Phthisis Prevention Commission was organized and in 1912 The Miners' Phthisis Prevention Committee appointed. This latter group made a very thoroughgoing study of almost every aspect of the diseases of the miners (169) (clinical, roentgenological, pathological, bacteriological and statistical), studied carefully the nature of the dusts and fumes and their production, looked into the ventilation in the mines, investigated the hygiene and sanitation both within the mines and outside them; and laid the foundation for the widespread improvement in conditions that has been so very striking in that region. Since the appearance of the General Report of this Committee in 1916 (66), which led to the formation of the Miners' Phthisis Medical Bureau, the health of those employed in this region is in a vastly improved state. It is a revelation to look through the series of annual reports of this Bureau and see what Watkins-Pitchford and his closely-knit body of associates have accomplished and what is still being done under the directorship of his successor, Irvine. Hertslet (84) recently gave an excellent description of the general hygienic and medical care of the native workmen in the mines there.

Rice (85) has reviewed silicosis historically and has alluded particularly to the progress made in the several mining countries. He emphasized especially the fact that with the introduction of machine drilling, a marked rise in the incidence of "miner's phthisis" followed and this in every country into which this tool was brought. He likewise noted a material improvement where ventilation and exhaust systems were in operation. In the United States the Bureau of Mines, the Public Health Service, and the Department of Labor have each done a great deal to study and remedy the situation.

II. TYPES OF DUST

Nature of dusts

Some dusts are injurious when inhaled; others may be inhaled for years with apparent impunity. It is obvious that the type of dust has much to do both with the seriousness of its intrinsic hazard and with its influence on pulmonary tuberculosis. It is generally conceded that of the organic dusts, none exerts a baneful influence with respect to pneumonoconiosis or tuberculosis; of the inorganic dusts, most are at least potentially dangerous.

1. Organic dusts. Organic dusts, that is, those of animal or vegetable origin, when inhaled sometimes cause fever, constitutional disease or protein intoxication, but they do not cause pneumonoconiosis, although as far back as 1672 de Diemerbroeck (48) reported pigmentation of the lungs in heavy tobacco smokers. It was noted in 1799 by Beddoes (14) that millers and others working in organic dusts are not predisposed to tuberculosis. Data presented by Hirt (87) (1871) showed that of all diseases among workers in the flax and hemp indus-

TABLE 1

HEALTH HAZARD	SYMPTOM, CONDITION, OR DISEASE TO LOOK FOR	OCCUPATIONS WHICH OFFER SUCH EXPOSURE
1. Organic dust	Dryness of nose, throat and mouth, cough, anaphylaxis, asthma, bronchitis, emphysema, tuberculosis	Bakers; beamers (textiles); blowers (felt hats); broom makers; brushers (felt hats); brush makers; buffers; button makers; carbonizers (shoddy); carders (textiles); card grinders (textiles); carpet makers; celluloid polishers; celluloid workers; cigar makers; cobblers; comb makers (celluloid); coners (felt hats); cork workers; cotton-mill workers; cotton twisters; curriers (tannery); devil operators (felt hats); doffers (textiles); feather curers; feather workers; felt-hat makers; fiber workers; finishers (leather); flax spinners; flour workers; formers (felt hats); fur carders; fur clippers; fur cutters; fur handlers; fur preparers; fur pullers; glove makers (leather preparers); glue workers; grain-elevator workers; grinders (rubber); guncotton pickers; hair workers; harness makers; heel makers (shoe); hemp workers; jute workers; knitting-mill workers; lace makers; lasters (shoes); leather workers; linen workers; match-factory workers; mattress makers; mixers (felt hats); mixing-room workers (miscellaneous); pouncers (felt hats); rag workers; roller coverers (cotton mills); ropemakers; rubber workers; sawmill workers; scourers, wood lasts (shoes); shavers (felt hats, furs, tannery); shaving-brush makers; shoddy workers; shoe-factory operatives; sifters; silk workers; softeners (tannery); spinners (textiles); starch makers; straw-hat makers; taxidermists; textile workers; tobacco rollers; tobacco workers; upholsterers; weavers; weighers; wood-last scourers (shoes); wood workers; wool carders; wool spinners; wool workers

tries only 2.3 per cent were pulmonary in nature. Pincherle (156) reported a high incidence of asthma and catarrhal changes among woodworkers—but no pneumonoconiosis, as also did Schilling (184) among cotton mill employees. A high mortality from tuberculosis among workers in the tobacco factories in districts near Mannheim has been attributed to the dusty employment. An investigation of the situation by von Müller and Berghaus (139) revealed the facts that (1) the factories were horribly unhygienic; (2) the workers were usually not robust on beginning work (stronger ones working elsewhere for better wages) and (3) tuberculous infection in the homes was an important factor in the epidemiology of tuberculosis of the district. According to Thorell (207), tobacco workers in Scandinavia are not unduly prone to pulmonary tuberculosis.

Organic dusts derived from the handling of grain are sharp, spiny, and rough, and lead to cough, sneezing, discomfort, etc. (McNair and Middleton (121)), but these authors made no mention of pneumonoconiosis. On the contrary, Albaugh (2) has very recently declared that wood dust predisposes to tuberculosis and that the dust particles may carry germs. A case of so-called tobacco pneumonoconiosis was reported in 1921 by Palitzsch (148). The disease was a very chronic, protracted pulmonary affection which was finally proved to be nontuberculous. Landis (110) in 1919 and more emphatically in 1925 (112) pointed out the fact that there is no evidence whatsoever—neither clinical, roentgenological nor pathological—that organic dusts can cause pneumonoconiosis. He based his conclusion in part upon an analysis of fifty autopsies of workers in organic dusts, not one of which had pneumonoconiosis. He did not conclude that such dusts might not carry tubercle bacilli or might not predispose to tuberculosis for there is a suggestion that the latter may be true, but he was insistent that organic dusts do not produce pneumonoconiosis and in that manner open up the way for the subsequent development of tuberculosis. Gade (59) likewise commented on this characteristic of organic dusts. Very recently Middleton (129) has described under the caption of "weaver's cough," an affection of a certain class of weavers of cotton cloth in England which is characterized by dyspnea, troublesome cough, slight expectoration, vomiting, sore throat, and fatigue. The disease had appeared several times in outbreaks, the one described involving 245 persons. In his judgment it may have been caused by an unidentified mold which was frequently found in the warp. It is worth notice in this connection that in 1848 Tersancky (201) described a disease among workers in factories where mushrooms were rendered into punk or other pyrotechnical sponge. The disease manifested itself by irritative cough, pleurisy, blood-streaked sputum, epistaxis, fever, malaise and excoriations of the skin. He attributed it to a growth of dried mold on the fungus.

In recounting occupational hazards Dublin and Leiboff (51) in a publication of the United States Bureau of Labor Statistics have submitted a list (as given in table 1) of the occupations in which organic dust is encountered.

2. Inorganic dusts. Inorganic dusts are so commonly the offenders in the production of disease and organic dusts so uncommonly so that the term "dust" has come to imply the former; in special circumstances where organic dust is involved it is so specified; therefore we have "dust" and "organic dust." Inorganic dusts differ radically in character. The following properties are said to determine the degree of harm they may produce.

a. Physical properties:
  1. The "hardness" or "softness" of the particles.
  2. Their size and
  3. Their shape.
b. Chemical properties:
  1. The chemical power of the particles as irritants.
  2. Their property of absorbing organic substances.
  3. Their solubility and
  4. Their chemical reaction.

a. Physical properties. With respect to the question of the "hardness" of dusts, Oliver (146) has stated that it is wholly the physical character of the dust that is important. Soft coal dust, he held, is much less harmful than hard coal dust, and that of hard coal much less harmful than that of rock, while dusts from silica and from siliceous material are quite injurious. He cited in this connection the work of Claisse and Joué (28) who exposed animals to smoke from burning turpentine for long periods and produced an extensive though delicate pigmentation of the lung; but the discoloration, even though extensive, was apparently quite harmless to the animals. Mavrogordato (126) compared the effects of the inhalation of coal, shale, "flue" dust, precipitated silica, quartz, and flint dusts, and found the most damaging results to ensue from the harder dusts. Landis (110) remarked that the severity of lung lesions varies "in accordance with the hardness, sharpness, and chemical composition" of the dust and that silicotic dusts may produce "serious damage to the lungs."

The researches of Watkins-Pitchford and Moir (224) have also thrown much light on the physical character of dusts. Upon studying silicotic lungs (from gold miners of South Africa) they found that by far the largest numbers of particles of foreign matter in pigmented lungs are smaller than one micron in length, that the mean measurement of 100 particles taken consecutively and drawn to scale was 6.13 by 2.18 microns, that no particle was longer than 13 microns, and that *the prevailing form of the particles in such lungs in general is narrow and elongated with one or both ends sharp and pointed.* They felt that phagocytes show a selective action for small and elongated forms. A polariscope was used in their work. Katz (99) has stated that particles smaller than one micron are less harmful than those a little larger, since they either lodge less readily or are more readily removed than particles which are about one micron.

It has been supposed that the sharp, angular particles lead to mechanical irritation by laceration and that such dusts could penetrate or be driven through the epithelium. (Ogle (144), Bandelier and Roepke (10), Rindfleisch (177), Traube (210), Watkins-Pitchford (221), General report (66)). Asbestos fibres are neither sharp nor angular yet they get through the epithelium and incite reaction as Oliver (147), Wood (236) and others have recently shown.

b. Chemical properties. Concerning the irritating properties of dusts, Mavrogordato (126) believed that the dusts which irritate the mucosa promptly upon introduction into the lung are the very dusts which do the least permanent injury. His feeling was that there is an immediate reaction to irritating dusts on the part of the respiratory epithelium, marked by an engulfing of the foreign elements by the epithelial cells, and that this is followed by a desquamation; these shed "dust cells" form a bolus to which, with mucus, other cells, dust particles and débris attach; these "plugs" are then spat up and in this way much of the foreign matter is removed before it ever actually reaches the lung parenchyma. The rate of elimination, he felt, is as important as the rate of intake. He suggested that silica is not necessarily a dangerous dust, especially if it be inhaled along with coal dust which attracts phagocytes to the alveoli and facilitates rapid elimination.

Haldane (76) agreed that the baneful influence of dusts in the lung is determined largely by whether the particles are removed from the organ or are retained in it, and, in seeking an explanation of this fact, suggested that it is those dusts which readily absorb other substances (water, tissue juices, etc.) that are most promptly removed from the lungs. Carbon, shale, and other like dusts possess this property to a marked degree; and he advanced the idea that these particles become increasingly attractive for phagocytes as they continue to absorb more substances, whereas, the more crystalline, nonabsorptive particles—flint, quartz, silica, etc.—are, in their nakedness, less attractive to the dust-carrying cells. Yet, as Gardner (63) pointed out, granite dust which contains "juicy absorbent particles" is associated with an unusually high mortality rate on the part of those breathing it. This idea presupposes that the inert dust particles reach areas where absorption of tissue juices is possible before phagocytes act upon them.

On the other hand, many believe that certain dusts, instead of absorbing body fluids, are dissolved by these. In his Milroy Lectures in 1915 Collis (34) called attention to the possible significance of the acidity of dusts. Collis may be quoted on this point:

> Silica dust then possesses certain qualities: (1) physical, (*a*) such smallness as permits the particles to be carried into the alveoli, and (*b*) such hardness and angularity as suggest that the particles can act as centers of irritation; and (2) chemical, (*a*) acidity which, owing to the presence of the element silicon, may render the particles capable of entering into and modifying the colloidal structure of protoplasm, and (*b*) smell, possibly due to a vapor, as yet undetermined, given off when silica is fractured. Only further investigation can determine which it is that leads the pulmonary connective tissue to proliferate, and whether the undoubted predisposition to pulmonary tuberculosis caused by inhaling silica dust is due to this proliferation.

The chemical aspect of this question has received a great deal of attention in the last few years by Gye and Purdy (75) Gye and Kettle (74), Kettle (101) and others. Gye and Kettle claimed to have demonstrated that silica is dissolved and absorbed after its entrance into the body, the soluble form then poisoning the body. If soluble silica, colloidal silicic acid, or insoluble silica be injected subcutaneously into animals, there develops an area of necrosis, surrounded by granulations and fibrous tissue which eventually replaces the necrosis and the entire area becomes a scar. The injection of carbon, iron, etc., leads to no such results, but mine dust arouses a similar response as also does insoluble silica oxide when enclosed in a celloidin sac and placed beneath the skin.

What of the influence of the absorption of this product upon tuberculosis? When silica and tubercle bacilli are injected together the bacilli are protected (apparently) by the coagulum and multiply rapidly. If animals be given "silica abscess" in one groin and some other irritative abscess such as that caused by turpentine, for instance, in the other and then if the animals be inoculated intravenously with tubercle bacilli, many more of the latter will be focalized in the silica than in the other abscess. These authors concluded that the silicotic lung tends to become tuberculous not because it is fibrotic nor because of any mechanical interference with flow of lymph, but because of the presence of the toxic silica.

Admitting that colloidal silica may damage tissue, Heffernan and Green (81) raised the question whether, if silica is a "protoplasmic poison," tubercle bacilli thrive in areas made necrotic by this substance. Silica exists in all vegetable foods and in the connective tissue of animals and man and certainly does not poison these tissues. They suggested that the action of colloidal silica solution on animal tissues is an adsorptive and coagulant one in which it acts not as a poison but as a colloid, absorbing body fluids, producing coagulation, agglutination, etc., because it is a colloid of great surface energy. Much of the dust we breathe is ultramicroscopic (Heffernan and Green (81)) and is near molecular size, where surface tension, surface energy and electric change are of much more importance than hardness, sharpness, and other physical properties.

The idea has also been advanced (Mavrogordato (127)) that once silica is taken into the cell it preserves the latter just as water glass (silica) preserves eggs and that these cells tend to agglutinate and form pseudotubercles.

There remain yet numerous unsolved problems as to the mechanism of damage from the inhalation of dusts. More careful work is needed for the elucidation of these questions.

The roll call of the trades which involve the inhalation of inorganic dust—a good number associated with a high incidence of tuberculosis—is a long one and has been given by Dublin and Leiboff (51) as shown in table 2.

3. Artificial abrasive dusts. Within the last few decades numerous artificial abrasives have been introduced into industry. These have silica in them but nearly all of it is in combination. They are exceedingly hard, and the wheels will outwear ten or even fifteen sand stones of equal size. The result is that the damage which such dusts inflict upon the lungs is relatively slight. Clark (30) (31) has reported upon the state of health of employees with an average of over 17 years' service in a manufactory of composition wheels, in the making of which silicon carbide and aluminum oxide are used. He found that all were healthy and that there was no unduly high incidence of pulmonary disease among them. He went so far as to state that men with arrested tuberculosis may work with impunity in these artificial abrasive dusts which are made chiefly from silicon carbide. The relative harmlessness of combined silica stands out clearly in some experimental work which I did with this dust (229). In these experiments guinea pigs were exposed to the inhalation of silicon carbide for more than three years and, at autopsy, very slight anatomical change occurred, and this exposure in no way modified the course of tuberculosis subsequently induced in the animals. More can be said concerning these dusts, however, after they have been in use a longer time.

4. Toxic dusts. There is also a group of what might be called *toxic* dusts such as lead, arsenic, etc., which produce a constitutional effect on the body after they are absorbed following inhalation. These dusts, although important from the standpoint of industrial medicine and public health, have little or nothing to do with the subject in hand for they neither cause pneumonoconiosis nor predispose to tuberculosis.

TABLE 2

HEALTH HAZARD	SYMPTOM, CONDITION, OR DISEASE TO LOOK FOR	OCCUPATIONS WHICH OFFER SUCH EXPOSURE
2. Inorganic dusts	Cough, dyspnea, pleuritic pains, hemoptysis, clubbed fingers, marked flatness of chest, deficient expansion (unilateral), dullness, diminished resonance, mucous râles, fibrosis, inflammatory condition of eyes, ears, nose and throat; colds, chronic catarrh of respiratory tract, chronic catarrh of digestive tract, pleurisy, tuberculosis	Acetylene makers; asbestos workers; basic slag (artificial manure) workers; battery (dry) makers; bed rubbers (marble and stone); bench molders (foundry); bevellers; bisque-kiln workers; bone workers; brick-makers; bronzers; buffers; burrers (needles); burr filers; button makers; calenderers (rubber); carbide makers; carbon-brush makers; carborundum workers; card grinders (textiles); casting cleaners (foundry); cement workers; charcoal workers (sugar refining); chargers (smelting); chargers (zinc smelting); chasers (steel); chimney sweepers; chippers; clay and bisque makers (pottery); clay-plug makers (pottery); color makers; compositors; compounders (rubber); concentrating-mill workers (lead and zinc); core makers; crucible mixers; crushermen (clay and stone); cut-glass workers; cutlery makers; cyanamid makers; diamond cutters; electrotypers; emery-wheel makers; engravers; fertilizer makers; file cutters; filers; flint workers; floor molders (foundry); flue cleaners; foundry workers; glass blowers; glass cutters; glass finishers; glass mixers; glaze mixers (pottery); gold beaters; gold refiners; graphite workers; grinders (metals); gypsum workers; horn workers; jewelers; junk (metal) refiners; lapidaries; lead smelters; lime burners; lime-kiln chargers; lime workers; linoleum makers; lithographers; marble cutters; masons; match-factory workers; metal turners; mica strippers or splitters; mica workers; miners; mixers (rubber); mixing-room workers (miscellaneous); mold breakers (foundry); paint removers; paperhangers; phosphate-mill workers; pit molders (foundry); planer men (stone, metal); plasterers; plaster of Paris workers; pneumatic-tool workers; polishers; pottery workers; pouncers (felt hats); pressmen (printers); printers; putty makers; putty polishers (glass); pyrites burners; quarrymen; rubber workers; sagger makers; salt preparers; sand blasters; sand cutters; sanders; sanding machine operators; sandpaperers (enameling and painting auto bodies, etc.); saw filers; scrapers (foundry); screen workers (lead and zinc smelting); sifters; sintering-plant workers; slate workers; slip makers (pottery); smoothers (glass); spinners (asbestos); stamp-mill workers; statuary workers; stone cutters (dry); stone cutters (wet process); sugar refiners; sulphur burners; table turners (enameling); textile-comb makers; tile makers; tool makers; top filers (foundry); tumbling barrel workers; weighers

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III. PATHOLOGY

It is patent that numerous inorganic dusts such as lime, cement and coal do but little harm to those who breathe them. In discussing the pathology of pneumonoconiosis, therefore, we will describe the condition brought about by the more harmful dusts, the most conspicuous of which is silica. But, as already stated, silica dust, to lead to pulmonary damage, must be of a certain sort. It must be *free, uncombined, crystalline silica.* Combined silica does but little if any harm. Irrespective of whether the physical and chemical characteristics of dust determine its capacity as a hazard to human health, the fact remains that silica exerts by far the most harmful results. The consideration will be largely concerned with silicosis since (1) it is by far the most important type of pneumonoconiosis with which we must deal and (2) the pathological reactions associated with it are typical of those set up by any of the dangerous dusts. The terms pneumonoconiosis and silicosis will be used interchangeably.

Human pathology

1. Natural defenses against inhalation of dust. It has been recognized that the upper respiratory tract possesses a very facile and, for ordinary purposes, an adequate mechanism for protecting itself and the lungs from inhaled dust. This portion of the system, especially the nose and nasopharynx, with its tortuous passages and its moist, hairy walls, is admirably constructed to arrest dust particles. This it does very satisfactorily as long as the air is not heavily laden with them. It acts efficiently until the surfaces become covered with dust, after which the former collect but little (Hill (86)). The moist mucous membrane of the nasopharynx, posterior pharyngeal wall and throat tend still further to filter out such particles as get by the more exterior barriers. The lining membrane of the trachea and bronchi is equipped with innumerable cilia which sweep the vast majority of dust particles that adhere to it back and up to the larynx whence they may be raised and spat out and only those particles which pass this series of formidable barriers are allowed to reach the alveoli. The clinical importance of nasal defects in predisposing to pneumonoconiosis is frequently lost sight of. This was first commented upon by

Saenger (183). But Ramazzini (165) in 1705, thinking that small stones might possibly grow into great stones, advised that "all possible Caution must be used, to avoid the sucking in of these minute Particles at the Mouth." Rivers (179) has stated that the rare cases of clinical anthracosis are "in colliers with wide, atrophic noses." It is a frequent observation in the mines of the Rand (225), in the Barre granite works and elsewhere that workmen with nasal defects are very liable to laryngitis just as mouth breathers in any environment are frequently subjects of bronchitis. In the experience of Watt, Irvine, Johnson and Steuart (225) mouth breathers are definitely more subject to silicosis than are normal breathers. There are occasional observers, however, (Jarvis (95)) who do not agree with this generally accepted thesis that mouth breathers develop more pneumonoconiosis. Ponies used in mines for years rarely have pneumonoconiosis, in all probability because of the tortuosity of the nasal passages (Rivers (180)).

A significant feature of pneumonoconiosis and one to be remembered is that it does not affect all people alike. It is the rule to find that in groups of workers of whom are similarly exposed, some will develop pneumoconiosis early, some will develop it late and some will not develop it at all. This phenomenon is manifest both clinically and pathologically, and knowledge of it is not infrequently of value. Such differences are doubtless bound up in some way with the anatomy and physiology of the upper respiratory passages. Gardner (60) has offered the hypothesis that an old, healed tuberculosis of the tracheobronchial lymph nodes may cause a partial obstruction of the lymphatics of this tissue which would lead to a more rapid development of lymph stasis and pulmonary fibrosis, once the individual took up a dusty occupation.

2. *The lymphatics and lymphoid tissue of the lung.* Most of the dust that finally reaches the lungs eventually gets into the "domain of the lymphatics," i.e., in or behind the alveolar and endothelial walls. This latter system is of paramount importance in any consideration of either pneumonoconiosis or tuberculosis and should be briefly described in this place. William Snow Miller in his very extensive studies of the histology of the lungs (134), (132), (131), (133), (135), has taught us a great deal about the lymphatic system in the lungs of

man and lower animal, and it is largely from his numerous and valuable contributions that I derive much of the data used in the description which follows.

The lung possesses a very intricate system of lymphatics and lymphoid tissue a description of which is easy to grasp if we bear in mind a few facts of the anatomy of the bronchi and blood vessels. The bronchi divide at close intervals from the bifurcation to the final anatomical unit or lobule. Branches of the pulmonary artery accompany the branches of the bronchus from large mediastinal trunk to very small vessel. The two lie in very close apposition and always toward the center of the lobule. They divide at the same points throughout the lung. The veins likewise divide at close intervals but they lie at a distance from the artery and bronchus. They are situated at the periphery of the lobule and are made up of many branches which form from the venous radicles at the dividing points of arteries and bronchi. Many of these veins pass along the interlobar septa. They extend to the pleura.

In the loose areolar tissue about the branching bronchi, arteries and veins an intricate system of lymphatics course which is quite as distinct as the arterial or the venous system. The lymphatics run in a most zigzag and tortuous manner, anastomosing with amazing frequency and thus furnish the lung with a facile drainage system. They extend as far along the bronchial and arterial systems as the atria—a part of the terminal unit of the respiratory tract. Peripheral to this point no lymphatics are discernible, but any foreign matter which reaches the tissue spaces anywhere in the lung eventually reaches the lymphatics, for this entire space drains into the lymphatic system. They also extend along the veins from the dividing points of bronchi and arteries to the larger venous trunks and from the pleura along veins which lie in the septa. These anastomose frequently to form larger and larger vessels which eventually reach the tracheobronchial lymph nodes at the hilum. The lymphatics of artery and bronchus are thus intimately connected at many points with those of the veins. The pleura likewise has a very extensive network of lymphatics, the branches of which connect freely with each other. This pleural system anastomoses at many points with deeper lymphatics already described, by trunks which pass inward, especially in the septa. These connecting trunks possess valves which are directed toward the pleura. There are thus two sets of lymphatics —a deep and a superficial set.

The flow of the lymph in the vessels which lie within a few millimeters of the pleura is toward that structure; the flow in the pleural vessels converges toward the tracheobronchial lymph nodes at the hilum. That of the deep vessels is a converging flow toward the hilum and reaches these same tracheobronchial nodes. These latter structures therefore are the eventual receiving stations for the entire lymph flow of the lungs and pleura.

At dividing points of the bronchi and, to a lesser degree, of the arteries and veins, at points where deep and superficial lymphatics meet and at the distal end of the alveolar ducts there are smaller or larger aggregations of lymphoid cells which are situated along lymphatics in such a way as to be essential filters. Therefore, they may collect and hold particulate matter—inert or viable—from the lymph and are thus frequently the seat of dust-deposit or infection, such as tuberculous infection. Similar aggregates of lymphoid cells are present in the pleura. It is well known, as mentioned by Pearson (154), Reisseissen (168) and others, and carefully studied by Miller (132), that there is an accumulation of dust in the lungs with increasing age. This accumulation is mostly in these masses of lymphoid tissue. These latter tend to become larger in response to the presence of the dust particles and represent the nidi from which the fibrotic nodules of the pneumonoconiotic lung arise. Miller (132) noted a causal relation between natural anatomical changes in the lung and the presence of dust and called attention to histological differences in the lungs at different ages. He observed a strikingly small amount of lymphoid tissue in the infant, more in the child, and a gradual increase with increasing age. He noted that this increase in the amount of lymphoid tissue was in close association with the increase in pigment, and concluded that the inhaled particles act as irritants which stimulate the proliferation of such tissue. Thus a vicious cycle may be established in which the irritant, dust, leads to enlargement of the lymphoid masses which, growing larger, become more efficient filters to hold more dust which, in turn, stimulates still further proliferation. The tracheobronchial lymph nodes are situated at the hilum and represent the "dumping ground" of the pulmonary lymphatic system and may be the final repository of relatively large amounts of dust.

In line with this anatomical fact Gardner (60) has, within the year, stated it to be his belief that obstruction to lymph flow, with thrombi of dust cells and dilated vessels, does not come about through simple accumulation of cells in the lymphatic vessels or by compression of these vessels from fibrosis, but rather from obstruction of the lymphatics in the tracheobronchial nodes. He offered a possible answer to the question of why people develop pneumonoconiosis at widely different periods of time after beginning occupation in siliceous dusts. He suggested that possibly in those who develop pneumonoconiosis early there exists an old, healed tuberculosis of the tracheobronchial lymph nodes which had led to a partial obstruction of the lymphatics; and which a comparatively short exposure to dust, too short to produce marked obstruction in normal nodes, would serve to greatly accentuate. This question is discussed later.

3. Agency of dust transportation. In spite of the anatomical defenses, dust eventually reaches many parts of the lungs. How are the particles carried from air space to tissue? The idea has been advanced by some (Sikorsky (191), Klein (102)) that particles may pass directly between uninjured epithelial cells. Traube (210) believed that the angular character of the particles enables them to pierce the epithelium, and Rindfleisch (177) stated that the impact of the inspired air was doubtless sufficient to drive the particles through this structure.

Policard and Doubrow (159) have contended that particles in the air of the trachea and bronchi are maintained in suspension in part by their electrical charge and in part by the continuous respiratory movements. The particles "settle out" upon the mucosa at a rate that is proportional to their weight, size and shape: the migration of particles into the pulmonary tissues is of the same nature as that of a needle under the skin.

But most workers oppose the view of penetration of the epithelium by particulate matter without the agency of some intermediate carrier and agree that the transportation is effected by cellular (phagocytic) activity. The nature of the phagocyte has occasioned much work which, however, has by no means brought unanimity of opinion. Whether the cell is a wandering cell, whether it comes from the blood or arises in the fixed tissues of the part, whether it is derived from vascular endothelium or alveolar epithelium—all these questions have been asked and each of these sources has been thought by different authors to be the proper one. For instance, the alveolar epithelium was held to be the "dust cell" by Knauff (104), Schottelius (185), and Ruppert (182) among the older writers, and more recently by Briscoe (22), Wainwright and Nichols (218), Sewell (189) and Mavrogordato (126) among others. It has seemed to several workers that possibly more than one type of cell could become a "dust cell." Arnold (6) thought that the bronchial and alveolar epithelium and "lymphatic wandering cells" are all capable of phagocytic activity. Oliver (146) agreed in part with Arnold, and, according to him, wandering cells of the pulmonary alveoli (which to him appear to be originally alveolar epithelium), may be dust carriers.[6] Oliver suggested that phagocytes acquire their load of dust in the alveoli from which they escape to the lymphatics through stomata. This idea was advanced, however, before Miller (130) showed that so-called "stomata" are artefacts which may be created at will by stretching or roughly handling the tissue. Watkins-Pitchford (221) wrote that the phagocytes are "catarrhal and leucocytic." The endothelium has been thought to be the source of phagocytes by many workers since 1869 when Slavjansky (193), by intravenous methods, showed that endothelial cells might find their way very quickly into the alveoli and become phagocytic for particulate matter in that place. More recently Klotz (103) held with Haythorn (80) that, while pigment may be found in a variety of cells, it is most commonly engulfed by an "endothelial leucocyte" which corresponds to the epitheloid cell of histological tubercle. Permar (155) supported this conclusion.

Determination of the type or origin of the dust cell is in the most favorable circumstances but little better than speculation unless selective, differential staining be resorted to. By such means Foot (58) who had previousy held the dust cell to be of endothelial origin (57) recently stated in a thoroughgoing study that it gives the same specific staining or impregnation reactions that the circulating monocytes do. Gardner (61) with a valuable technique for vital and fixed tissue staining has concluded that the septal cells, belonging to the group of clasmatocytes, are the parent cells of the alveolar phagocyte. Wislocki (234) asserted that it is principally the clasmatocyte which phagocytes carbon particles in the lungs.

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[6] Oliver made an interesting suggestion when he stated that these large phagocytes which lie free and loose in the alveoli, sometimes containing dust particles, sometimes devoid of such matter, are normal inhabitants of the alveolar spaces.

In this perplexing question it is very difficult to find sufficient agreement for a perfectly clear, crystallized opinion. I have felt from my own observations (231) that there was probably more than one type of cell concerned but, in these studies, morphology was the only criterion and this is an insufficient prop. The data given by Gardner, Foot and Wislocki all seem well controlled and probably represent an approximation to the true state of events. Drinker (49) has presented a good review of these questions.

4. *Elimination of dust from the lungs.* Elimination of dust from the lungs (to the tracheobronchial nodes) has already been briefly discussed. When one knows something of the anatomy and physiology of the pulmonary lymphatic system, it becomes perfectly obvious that the lymphatics constitute a very important if inadequate means of elimination. Lymph flow in all parts of the lung is eventually toward the hilum.[7] Some particles penetrate the walls of the lymphatics and come to lie in the areolar tissue in which the latter course, and there act as irritants. Some are filtered out by the lymphoid masses at dividing points of bronchi and vessels. Those that are carried along the sinuous lymphatics without becoming arrested by lymph mass-filter or tortuosity of channel eventually reach the hilum. According to Gardner (62) dust cells gradually accumulate around the lymphatics at the alveolar ducts and at these points are taken into the lymphatic system over which route they are carried haltingly toward the tracheobronchial nodes.

Another route of exit for dust and dust cells is through the bronchus and trachea. The dust is ingested by phagocytes which wander back to bronchi along which they are carried by cilia to the outside world along with mucus and débris. In this connection a recent observation should be mentioned. It has been found (Willis (228)) that in the rabbit's lung there are numerous areas of thinned out, nonciliated bronchial epithelium which overlie masses of lymphoid tissue. Dust cells have been seen in and apparently in transit through, these thinned areas from lymph node to bronchial lumen.

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[7] Cunningham, R. S.: Contributions to Embryology, Carnegie Institute of Washington, 1916, iv, no. 12, Publ. no. 224. Cunningham has shown that the lymphatics of the diaphragmatic pleura, in the foetus at least, communicates with the lymphatics of the peritoneum.

That the rate of elimination is as significant as the rate of intake has been emphatically pointed out by Haldane and by Mavrogordato. This is a matter of considerable importance and one which needs much elucidation. Fenn (54) has shown that leucocytes ingest carbon much more rapidly than they do silica.

It is possible though highly improbable, that dust particles are absorbed by the blood and are thus removed from the lung. Riddell (176), found fibrosis and pigment in the spleen and liver of a quarryman with a rapidly developing fatal pneumonoconiosis. However, what we know of the blood and lymphatic system indicates that the lungs tend to be the dumping ground of the body with not very facile eliminating faculties.

5. *Pathological picture.* Occasional autopsies were done on workers in dust a long time ago. For instance, de Diemerbroeck (48) in 1672 made the following unique observations (as related by Ramazzini (165)): "Diemerbroec gives a curious relation of several stone cutters who died asthmatic, and were opened by him; in whose lungs he found such heaps of sand, that in running the knife through the pulmonary vesicles, he thought he was cutting some sandy body." When autopsies came to be performed with more regularity, pathological observations on pigmented and fibrotic lungs began to appear with some frequency. Many of these are clearly described but the nature of the underlying etiology was poorly understood. Until comparatively recently several different diseases of the lung—tuberculosis, neoplasm, melanotic sarcoma, pneumonoconiosis, etc.,—were classified under the term "phthisis."

The evolution of the completed pathological appearance in pneumonoconiosis is a very slow, progressive one. Dust cells are irritants. These settle irregularly and intermittently in the several parts of the lung and gradually accumulate along lymphatics and in lymph nodes, where very insidiously they arouse the body's reaction, the end result of which is fibrosis. Greenhow (72) presented several cases of pneumonoconiosis and gave a good description of the pathology (especially gross) of the condition. According to the general report of the Miners' Phthisis Prevention Committee of South Africa[8] for 1916, the dust cells appear in definite clumps in the small masses of lymphoid cells, where their presence incites the proliferation of fibrous tissue, which finally results in fine, beaded, irregularly nodular thickenings occurring at intervals "on the course of the perivascular and peribronchial lymphatics." With increase of this fibrous tissue, there is a gradual obstruction of the lymphatics and a consequent further accumulation of the dust cells and a more diffuse fibrosis, which is seen in the alveolar septa and the adventitia of small bronchi and blood vessels (same report). This excellent presentation further points out the fact that gradually the subpleural lymphatics become thickened and that the tracheobronchial nodes develop fibroid changes early, soon after the thickening process has extended from the adventitia of the smaller air tubes and blood vessels to that of the larger ones. "*We find that the distribution of the silicotic process is that of a ramifying fibrosis*, which follows the distribution of the lymphatics accompanying the ramification of the bronchial and vascular trees, from their origin within the lobular region to the termination of the lymphatic system in the bronchial glands." The process is slowly progressive and produces (1) "thickening of the alveolar walls, with constriction and perhaps obliteration of the alveoli, and with catarrhal change, (2) thickening of he interlobular septa and (3) a more or less generalized fine thickening of the pleura and subpleural connective tissue."

The beading already mentioned represents enlargement and fibrosis of the masses of lymphoid tissue which are sandy; these nodules gradually become enlarged and densely fibrotic; they then coalesce and in this way nodule and diffuse fibrous process ultimately distort and replace much of the normal lung tissue. In the absence of the enlarging nodules the diffuse process ultimately effects this same result. Histologically these fibrous nodules are seen to be composed of concentric layers of connective tissue obviously laid down about pigmentary deposits. At first microscopic in size, they gradually increase until they may have a diameter from that of a millet seed to that of a small pea and at these stages correspond to the so-called "snowstorm" stage as seen by x-ray. The periphery of these nodules is always fibrocellular. They may increase in size and number as the process becomes older (a matter of years) and, if thickly sown, they may coalesce to form areas of massive fibrosis in which shadows of the original nodules are readily detectable. Nodular reactions occur more commonly in persons who have been exposed continuously for a relatively long number of years rather than in those who work intermittently in the dust.

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[8] The report gives an excellent general description of Miner's Phthisis, and from it I have drawn freely in preparing this and some of the subsequent sections.

Not all advancing fibrosis comes about from coalescence of nodules, for it may and most frequently does come about as a further development of the diffuse fine fibrosis. Associated with these changes is a gradual peribronchial and perivascular thickening in which there is more or less infiltration with dust. The engrafting of tuberculosis upon a silicotic process is a very potent factor in leading to an extensive fibrous consolidation.[9] Chronic nontuberculous pneumonia may likewise lead to such a result.

However, in places not thickly set with nodules or not greatly involved in a diffuse fibrosis, the pulmonary tissue retains a fairly normal appearance save for some emphysema and congestion, for a compensating emphysema develops in the less affected areas of the lung and "as a consequence, not only is the respiratory capacity directly reduced by obliterative changes, but the capacity of the lung to expand during inspiration is impaired," and this explains the dyspnea, "the cardinal symptom of silicosis."

"*A true silicotic nodule does not show caseation.*" This is a statement made by Watt, Irvine, Johnson and Steuart and is one which, while true in by far the largest number of cases, has had numerous exceptions taken to it. Large areas of massive fibrotic consolidation, sometimes break down at the center even when tuberculosis is not a complicating factor. This is not common and is presumably brought about by inanition of the part.

In the early stages the tracheobronchial lymph nodes are enlarged and discolored and crowded with dust cells. In the intermediate stages these structures contain much pigment, fewer cells and a good deal of fibrous tissue. The nodes are not larger than in the early stages. When the process in the lung is advanced, there is a total absence of cells and a very great deal of pigmented and white, dense fibrous tissue. The nodes are enlarged and may suggest fibromata.

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[9] See page 445.

Where pneumoconiosis is a compensatable disease, as it is in South Africa, liability to compensation has led to standardization of criteria on which a pathological diagnosis of the affection may rest. Criteria as follows have been laid down for the post-mortem diagnosis of silicosis (Watkins-Pitchford, (223)): (1) Lesions must be specifically those of silicosis and must be visible to the unaided eye and palpable to touch (so microscopic evidence alone does not constitute a diagnosis); (2) lesions must be numerous enough for one nodule to be present in each area of five square centimeters of pulmonary tissue, provided there is no evidence of silico-tuberculosis. In the latter instance compensation must be granted even in the absence of signs. Some such criteria should be adopted in the various countries where dusty trades exist and should obviously vary, depending upon the type of dust, its effect upon the lung, etc.

The sputum and material from lung puncture of people with asbestosis has been recently studied by Stewart and Haddow (197). They found characteristic yellow bodies, called "asbestos bodies," in this material, the nature of which was not apparent. Gloyne (67) stated that these bodies were made up of a deposit, possibly blood pigment, about the fiber.

Pathology of pneumonoconiosis with tuberculosis superimposed

It is not enough that the miner with pneumonoconiosis should be the subject of that disease alone, but many such people sooner or later experience, as an end result, tuberculosis engrafted upon the pneumonoconiosis. Tuberculosis may occur at any stage of pneumonoconiosis, but the acute types of the disease such as pneumonia and miliary tuberculosis are less commonly seen in the later stages of pneumonoconiosis, possibly because lymphatics are obstructed. In *early stages*, chronic pulmonary tuberculosis runs its usual course, but appears definitely to hasten the progress of the silicotic process, especially in the vicinity of the infection (Watkins-Pitchford (221)). Also the infective process may be greatly changed as a result of the surrounding fibrosis, and the tuberculous area may become the dense, fibrotic, pigmented mass which is the characteristic appearance of "massive fibrosis." In *later stages* the typical characteristics of each disease are modified, the degree of modification depending upon whether tuberculosis predominates ("tuberculo-silicosis") or pneumonoconiosis predominates. The mixed lesion growing out of tuberculosis and silicosis is the most common origin of the massive, fibrous consolidation in advanced silicosis (221) (66) (175). Such areas, when tuberculosis plays a part in their origin, are larger than coalesced silicotic nodules, they may be associated with occasional isolated areas of typical tuberculosis elsewhere in the lung; they occasionally have some caseation in early stages; they often have cavitation later. Tubercle bacilli may be found in these areas. Histologically, the appearance of these lesions is not that of ordinary tuberculous bronchopneumonia. "The typical structural arrangement of the tuberculous lesion appears to be overwhelmed by an excessive development of fibro-cellular and, later, of fibrous tissue" (Watt, Irvine, Johnson and Steuart). The pleura is thickened and often bound tightly with adhesions so as to make removal of the lungs impossible without tear.

It is thus clear that tuberculosis may occur in two forms when in association with pneumonoconiosis. These are: (1) Apical and unilateral with downward spread just as in a nonpneumonoconiotic individual; (2) Nonapical, often bilateral, but asymmetrical and often massive. With respect to the underlying factors in the production of these diverse types Gardner (60) has raised the question as to whether the worker who had an apical lesion before dusty employment began may fail to experience normal or expected healing of the area which later, sometimes years later, may develop into typical tuberculosis such as is seen in nonpneumonoconiotic folk. Similarly he suggested that the "atypical" form might arise as a new infection or reinfection and might be thought of as "industrial infection." It is an interesting hypothesis, particularly since the massive areas so closely resemble the lesions produced by reinfection. But it does not explain why almost uniformly the tuberculosis in silicotics comes late in life. If it were a new infection, it should appear at a wide range of ages.

According to Watkins-Pitchford (223), the nodules in uncomplicated silicosis consist of gray-black pigment and fibrous tissue and, as time goes on, become more encapsulated so that they may "shell out" of the capsule as small black pearls. In persons without tuberculosis, and after the lapse of many years, the nodules tend to disappear, the fibrous tissue becoming absorbed and the silica eliminated. When tuberculous infection is superadded, the result is pathologically different from that of uncomplicated silicosis in that the distribution of pigment becomes unsymmetrical and is increased about the focus of disease, which appears succulent and steel gray and not as the familiar lesions of ordinary tuberculosis, because characteristic tubercles are wanting. The young gray fibrous tissue is prone to necrosis and cavitation.

Experimental pathology

What appears to be the first experimental proof that dust may be inhaled into the lungs was made in 1862 by Villaret (215) who exposed rabbits to the inhalation of carbon and porphyrin in bags. At the end of the short experiments of a few hours he found very little dust in the pink lungs, only a few particles in the larger bronchi and great quantities in the stomach and intestine. In the experiments in which inhalation was continued for nine days he detected many particles in the lungs, intestines and portal blood. Five years later Knauff (104) devised clean-cut experiments in which he exposed certain dogs to the inhalation of smoke and others to an air-suspension of ultramarine blue for varying periods of time and subsequently recovered particles of these substances from the lungs. He thus unequivocally demonstrated that particulate matter could be inhaled into the lungs with the inspired air. Since these publications appeared a great deal of experimental work has been done. Konradi (107) confirmed Knauff's work in 1869. Arnold (6) made a very extensive study of experimental pneumonoconiosis. The study was published in 1885 and it is a detailed account of the pathology of experimental pneumonoconiosis. He exposed dogs and rabbits to various dusts for considerable periods of time and found accumulations of dust in the alveoli and their septa, in the lymph nodes and islands of lymphoid tissue throughout the lungs, and in fibrous nodules which develop in the lungs in response to the continued presence of irritating dusts. He observed dust particles *in* the lymphatics very infrequently.

The capacity of different dusts to lead to different results when inhaled is well shown in experiments. For instance, the innocuity of carbon and coal dust has been pointed out by numerous observers. Claisse and Joué (28) in 1897 exposed animals to smoke from burning turpentine. After prolonged exposure, the animals developed extensive though delicate pigmentation of the lungs which, although extensive, was apparently altogether harmless to the animals. Wainwright and Nichols (218) (in an insufficient number of animals) found that guinea pigs exposed to the inhalation of coal dust and then infected with tuberculosis developed the disease of the abdominal viscera but not of the lungs. They felt that coal dust exerted a distinctly protective influence and that the fibrosis which developed in response to the dust aided in "resisting" tubercle bacilli. It has been observed that guinea pigs tended to accumulate coal dust in the lungs only slowly and gradually and that when infected with virulent tubercle bacilli after exposures of a year's duration, they developed slightly more pulmonary tuberculosis than control animals. Such animals, however, rarely had more pigmentation of the lungs after a year's exposure to heavy clouds of dust almost daily than did normal, non-dusted animals that had lived in the laboratory for two years or longer and had spontaneously acquired its pulmonary dust (Willis (230)). This led to the belief that the lungs probably need a certain amount of stimulus (presence of a certain amount of dust) to initiate active elimination and that when dust reaches the lungs in small increments it is less likely to be eliminated than when it reaches these organs in larger amounts. This thesis, however, has not been proved. Mavrogordato (126) found that the dusts which were promptly eliminated (e.g., coal,) are the dusts which do no harm.

Other dusts that are clinically harmless, such as lime and cement, have been proved experimentally to exert no baneful influence either upon normal animals or on those that have tuberculosis. Nagai (141), Coutière (41) and others exposed normal and tuberculous animals to lime dust and observed that the dust produced no effect of any sort on the normal lungs and none on the course of pulmonary tuberculosis. Tucker (212) had essentially similar results from the exposure of animals to the inhalation of cement dusts. His animals were normal at autopsy.

On the other hand Cesa-Bianchi (26) exposed guinea pigs to the inhalation of talc, gypsum, coal, cement, etc., and found that, after infection with tubercle bacilli, the animals developed a marked degree of tuberculosis with extensive cavity-formation, while normals, when infected similarly, showed little or no tuberculosis in the lungs. The reason for such a great difference in results from those of the normal animal is not clear. These results of Cesa-Bianchi have not been confirmed. Beattie (12) felt that the fibrosis resulting from the body's reaction to dust protects against the spread of tuberculosis in the lung.

Steel and porcelain in some of the experiments performed on rabbits by Jötten and Arnoldi (96) exerted a detrimental effect upon tuberculosis. Lime exerted no such effect. In their judgment coal dust had no bactericidal effect, although its effect upon pulmonary tuberculosis remained equivocal. Flint dust, and coal, china clay, feldspar, earthenware, pure amorphous silica, pure flint, coal, shale, ignited shale, dried earth and ignited earth have all been used experimentally in guinea pigs by Carleton (24) in periods of exposure of from a few minutes to nearly two years. He concluded that coal dust is rapidly phagocytosed and eliminated; that shale is comparatively harmless; that amorphous silica is more harmful than crystalline silica; that china clay dust, felspar, and ground earthenware are potentially dangerous and that the harmful dusts are those which are removed but slightly or slowly from the lungs.

When animals are exposed to the more siliceous dusts such as granite, (Gardner (63), Gardner and Dworski (65)) generalized pigmentation and fibrosis of the lung develops, many more tubercles are present and, when cultures of low virulence are used, they are slower in resolving.[10]

It is well known that workers in marble quarries, tombstone cutters, and others who handle marble experience none of the usual dust hazards which are bound up with similar occupation in other dusts. Experimental work with this dust has led to a similar conclusion in so far as the effect on the normal lung is concerned. But it is different when the animal has been infected previously with tubercle bacilli. Gardner and Dworski (65) exposed guinea pigs to the inhalation of marble dust for varying periods of time up to nearly a year. Most of these were infected with tubercle bacilli of low virulence, some prior to the first exposure, some during exposures and some subsequent to the last exposure. A very large proportion of the dust particles was dissolved, so that only an occasional particle of silica or small amounts of amorphous material remained in the lungs of the normal animals. The insoluble matter led to a moderate degree of silicosis after long exposures but marble of itself did not affect the lungs, and in such lungs, tubercles set up by a strain of low virulence became "chronic" and receded slowly. Animals with preëxisting tubercles in the lungs showed some increase in calcification after exposure. Animals exposed to marble dust had from two to four times as many tubercles in the lungs as normal, nondusted controls. When a more virulent strain of tubercle bacilli was used, extensive fibrosis developed.

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[10] Since this paper went to press, Gardner (Am. Rev. Tuberc., 1929, xx, 833) has published a very convincing piece of work in which he showed that inhalation by guinea pigs of several kinds of dust caused a very definite reactivation and progression of what is ordinarily regressive, healing infection (R_1 infection). Roughly, three fourths of the animals exposed to quartz dust, one third of those exposed to carborundum and one fourth of those exposed to granite dust developed progressive disease. He commented on the significance of such observations when thought of in terms of clinical reactivation of an old area of tuberculosis in people working in dust.

There is abundant evidence from experimental work to confirm the oft-repeated observation that when tuberculosis becomes established as a complication of pneumonoconiosis, the outlook is grave and the course often rapid. What the underlying factors are we do not know. It is evident that tubercle bacilli and particulate matter tend to become located in the same anatomic situation, and the presumption is that the same mechanical and physiological forces which tend to place the one foreign body operate in the same manner toward localizing the other. There is a striking coincidence in the location of both dust and bacilli in the lymphoid tissue associated with air tubes and blood vessels. In the pleura there is a discernible relation. The subpleural tubercle is frequently though not by any means always at the margin of the secondary lobule in the usual anatomic position of the subpleural collections of dust.

There is probably some basis for the contention of Beattie (12), Haythorn (80) and others that the fibrosis which develops in response to the presence of certain dusts would tend to limit the spread of the infectious process and should be regarded as protective in that sense.

But the converse is equally true; namely, that the fibrosis would also tend to focalize and to hold bacilli because lymph drainage would be interfered with; so, while one would find *less extensive spread* of infection from a focus in a dusted lung, he might expect to find a *larger number of foci and possibly larger foci* scattered through the organ.

1. Intercurrent disease in experimental animals. It is a fact well known among those who have experimented with the inhalation of dust that the mortality rate of the experimental animals from various diseases is usually considerably higher than that of normal, non-exposed animals. For instance, Arnold (6) reported a mortality among his experimental rabbits and dogs which ranged from 8.6 to 33 per cent. The deaths were from several pulmonary diseases but by all odds pneumonia was most frequently encountered. In numerous instances in both rabbits and dogs after inhalation, the lungs revealed small miliary nodules which were strikingly like small tubercles in distribution and gross appearance. These were not structurally like tubercles, however. None of them revealed tubercle bacilli. It would appear from Arnold's description that these structures were incidental and not the cause of death.

2. Recapitulation. Although the normal defenses of the respiratory tract prevent the inhalation of many particles of dust, people working in air charged with dust eventually inhale considerable amounts of the latter, a good deal of which is carried by dust cells to the lymphatic system and through this to the interstices of the lung where it tends to accumulate and to incite the formation of fibrous tissue which may eventually obliterate most of the normal lung structure and materially predispose the person to tuberculosis.

The gross appearance of the silicotic lung is characteristic. It is stiff, inelastic, pigmented and adherent. It offers resistance to the knife which cuts it with a grating noise, the incision yielding a mottled surface of pigmented nodule, often grown around a bronchus or blood vessel, much pigment, diffuse fibrosis, thickened interlobar septum and thickened bronchial and vascular walls. Occasionally in the absence of complicating tuberculosis and often in the presence of the latter, there may be large, densely fibrotic masses which occupy much of a lobe or a lung and which may be caseous or cavitated at its center.

Histologically, the picture is that of extensive nodular, diffuse, or massive fibrosis with occasional areas of typical tuberculosis and with tubercle bacilli frequently present in the caseated areas of massive fibrosis.

Although usually widespread, the lesions are less numerous in the anterior margins, where motion is considerable, than elsewhere.

IV. DIAGNOSIS

Uncomplicated pneumonoconiosis

Pneumonoconiosis, generally a chronic disease, may develop and pass slowly or rapidly through successive stages until the completed picture is presented. Because of this fact, classification of the disease by stages has been repeatedly attempted. The classification of silicosis legally adopted in South Africa has been given as follows by Watkins-Pitchford (220):

Anteprimary stage: The earliest detectable signs, usually unassociated with symptoms or incapacity to work.
Primary stage: Well-developed specific signs associated with some loss of physical capacity, but the latter not necessarily serious or permanent.
Secondary stage: Well-developed specific signs associated with incapacity to work. This stage is nearly always translated from a primary stage by engrafting of tuberculosis.

These stages correspond essentially to those designated as the first, second, and third stages in this country. Other classifications have been devised in other countries but they all embrace essentially the group listed above (Nicholson (143) for England), (Purdy (164) and Smith (195) for Australia).

It has been stated frequently, especially by South African workers, that the evolution of simple silicosis is greatly modified and in the earliest stages is hurried into clinically recognizable disease by the presence of previously undetected tuberculosis. Thus it is seen that not only does pneumonoconiosis predispose to the development of tuberculosis but that tuberculosis hastens the development and course of pneumonoconiosis.

1. Physical diagnosis. The symptoms and signs in pneumonoconiosis grow so directly out of the pathological changes that they are very easy to comprehend, once the latter is appreciated. The onset is very slow and gradual and varies a great deal with the type of dust inhaled. For instance, symptoms may appear within the first five years of exposure to sand, quartz, and other siliceous dusts, although the average period before symptoms in such dusts (in South Africa) is nine or 10 years. They ensue in from 10 to 20 years in those who breathe granite dusts, in 20 to 25 years in pottery workers; and frequently coal miners work 30 or 40 or more years before the appearance of symptoms which not infrequently never develop among such workers.[11] The rate of development of symptoms is dependent upon the intensity and continuity of the exposure, the number and fineness of the particles, their relative freedom from inert dusts, e.g., coal or shale (Mavrogordato (126) Haldane (76)), the anatomy of the upper respiratory tract, possibly the presence of old tuberculosis of the tracheobronchial lymph nodes (Gardner (60)) and the presence of tuberculosis of the lungs. The slow, leisurely development of the fibrosis in pneumonoconiosis, with its gradual encroachment upon pulmonary physiology, must obviously bring about at first only insidious changes in respiratory function, which for a long time are not detectable clinically. It is one of the striking features of uncomplicated pneumonoconiosis that the patient may be asymptomatic for a long time, in some instances and in the case of certain dusts, many years, after both clinical and roentgenological signs are present. This disproportion between serious anatomical and radiographic signs and lack of symptoms surprises the examiner over and over again. Observers agree that the earliest symptom to appear, the most persistent, the most conspicuous and distressing is *shortness of breath* which at first is noted only on exertion. As the affection gradually progresses, this symptom becomes more pronounced and more easily elicited and is associated with a slight, non-productive cough, transient pleural pain and frequent "bronchial colds." Still he looks and feels well but the dyspnea has begun to limit his capacity to work. Later, all these symptoms become exaggerated, the dyspnea may be extreme, the cough moderately productive and troublesome, especially in the morning, and for the first time the patient begins to lose weight and strength. Finally the shortness of breath may became so marked that any physical activity, even walking, is out of the question and the patient must sit with his hands resting on his knees to give added support to his body, which leans forward in manifestly labored, quickened breathing with all the accessory muscles brought into play. This is said to be the end-picture, especially of the granite workers in Vermont.[12] The vital capacity of coal miners has been studied by Myers (140) who found that such workers, even after more than 20 years of mining, had an approximately normal capacity. Similar studies on persons exposed to silica dust have not been done. Even though tuberculosis is an exceedingly common complication, pleural effusion is very rare among this class of workmen (203).

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[11] As pointed out elsewhere, a very large proportion of workers who are exposed to dust, even siliceous dust, never develop pneumonoconiosis. This is an important consideration.

The signs are at first slight and indecisive. The chest has a normal conformity and is normally resonant, but expansion is somewhat limited and the breath sounds distant. In intermediate stages the chest is rigid, the front smoothy flattened, the shoulders raised, expansion is definitely limited and respiration predominantly abdominal, the percussion note is fairly resonant but patches of dulness from thickened pleura are not uncommon, and the breath sounds are distant; the chest is usually dry but occasionally a few râles may be heard. The important signs in late stages of the disease have been given as follows by the Miners' Phthisis Prevention Committee (66): (1) Rigid chest, with shoulders raised, fixed in partial expiration and with marked limitation of expansion (visible and measured); (2) Reduction of amplitude of the breath sounds, shortening and roughening of inspiration and prolongation of expiration which remains vesicular; (3) Dry chest. Crepitant râles suggest some infective process; (4) Friction rub. "The disease shows itself by increasing shortness of breath on exertion, by impaired expansion, an altered conformation of the chest, impaired air entry, and characteristic alterations in the breath sounds, and it is typically 'dry.' The presence of this characteristic complex justifies a diagnosis (of silicosis)."

There is no fever, and, except in extreme degrees of the disease, no tachycardia, marked asthenia or expectoration, all of which may quickly appear upon the supervention of tuberculosis. The lips are usually cyanotic, the mucous membrane of the nose pale. There may be chronic reddening of the laryngeal mucosa. Haemoptysis is rare and suggests the probability of a superimposed tuberculosis. The red blood count and the hemoglobin may be high from the cyanosis which at times is extreme.

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[12] This is the picture that has been given to me, but I cannot state whether it is overdrawn. Personal communication from a physician who has worked in the region.

Numerous other pulmonary diseases, notably bronchitis, emphysema and asthma, are prevalent in workers in dust and may occasionally offer diagnostic difficulties. In this connection it is very helpful to remember that the silicotic chest is usually *dry*. How much the dust has to do with the etiology of these nontuberculous diseases one does not know. Within the confines of the subject under review, a detailed discussion of this question is not germane.

2. Roentgenological diagnosis. This part of the question is discussed below under the caption—Tuberculosis and Pneumonoconiosis.

Tuberculosis and pneumonoconiosis

Year by year the reports of the Miners' Phthisis Medical Bureau indicate an appreciable diminution in the incidence of silicosis and of silicosis with tuberculosis, the latter now having well-nigh reached the vanishing point. The later reports point out the fact that as this decrease occurs, there is a concomitant increase in the incidence of simple, uncomplicated tuberculosis. This shift has now brought about a noticeable change in the type of clinical disease and pathological alteration. In earlier years the pulmonary changes were usually those produced by dust and infection; the former usually predominant. Now the tuberculous element predominates. On this point the last report of the Bureau (175) contains the following pertinent remarks:

> "Miners' Phthisis," as we know it, is essentially the product of two factors, dust and tuberculosis, and there are two pathological and clinical types of the disease, according as the one factor or the other is predominant in its causation. During the first fourteen years or so, which succeeded the turn of the century, the prevalent type of silicosis met with was one in which the dust factor was predominant. It was characterised by large heavy lungs, in which an excessive development of pathological fibrosis overwhelmed and sometimes wholly obscured the evidence of co-existing infection, and frequently tended to retard the development of the latter. The great diminution in the dust content of mine air, effected by the preventive measures directed against the production and dissemination of dust,

which has contributed very largely to bring about the decrease in the true production of silicosis, already discussed, has had another and less satisfactory result. It has brought about a change in the prevalent type of "miners' phthisis" to one in which the influence of the tuberculous factor has become more obvious, alike at the outset and throughout the course of the disease. The returns just quoted afford objective evidence of this fact. The direct effect of dust in producing excessive fibrosis, and the further effect of the latter in tending in many cases to retard the development of tuberculosis, have been diminished. The disease has assumed a relatively more infective and therefore, it would appear, a relatively more progressive type.

Although this change in type of "phthisis" has been conspicuous in South Africa, it is not altogether confined to that region, and there is an appreciably large incidence of ordinary tuberculosis among workers of several sections where marked improvement in dust-elimination obtains. With this, however, there is an associated decrease in the total incidence of this disease. It may be deduced from this that there has been a concomitant shift in the character of the signs and symptoms. Such has also been the case, with the more frequent appearance of signs and symptoms of ordinary tuberculosis. But there is still a superabundance of cases of the two diseases in co-existence.

1. Physical diagnosis. Tuberculosis may complicate pneumonoconiosis at any stage but it more commonly does so when the latter disease is advanced. When it supervenes in early pneumonoconiosis the clinical picture is, as would be expected, predominantly that of the infection. Symptoms suggest tuberculosis, and physical signs and clinical course are usually clearly those of this disease. When it comes on in later stages of pneumonoconiosis the clinical picture is characteristic but is like neither disease when uncomplicated. Usually upon developing tuberculosis the patient rather rapidly loses weight and strength; his temperature rises and his pulse rate accelerates; his cough becomes definitely increased and his sputum more abundant and often streaked with blood; pleurisy is common; asthenia and exhaustion become extreme and the patient dies. Signs of consolidation are often present.

Many patients, however, suffer an intensification of the symptoms of pneumonoconiosis under which they have been laboring and go to death (usually rapidly) with dyspnea, orthopnea, pulmonary edema and often cardiac failure. Still other patients with both diseases may run a very chronic course. These are relatively few in number. It cannot be too strongly emphasized that *repeated, careful examinations of the sputum for tubercle bacilli* (see Landis (111)) *constitutes one of the most, if not the most, important factors in the diagnosis of tuberculosis added to pneumonoconiosis.*

Many people in late stages of pneumonoconiosis eventually experience tuberculosis as a complication. This, however, is not true of those in earlier stages. The prognosis in people in whom tuberculosis is engrafted upon *early* pneumonoconiosis is not, when properly treated, greatly worse than that in people with tuberculosis alone. When the infection comes to those in later stages, however, the outlook in a very large majority of cases is very bad "and the disease is fatal within no long time."

Loss of weight is a conspicuous sign among the native laborers in the mines of South Africa. Two-thirds of those with uncomplicated tuberculosis show it. It is a sign of such importance there that it suggests automatically a special examination (174).

2. Roentgenological diagnosis. There is a well-recognized tendency in medicine for the clinician to depend upon the roentgenologist for his diagnosis, especially in diseases of the chest. This situation is bad for clinician, roentgenologist and patient and cannot be too severely condemned. The x-ray is of invaluable aid in clinical medicine when used coordinately as one of the manoeuvres in the general survey of the patient. It is especially valuable in the detection of pneumonoconiosis because this disease will cast characteristic shadows in the film long before it will disclose itself by physical signs. It is likewise very valuable in studying the course of the disease. Watt, Irvine, Johnson and Steuart (225) unhesitatingly stated that the x-ray plate is of great value in their medical work among the miners of the Rand. They remarked: "We are fully of opinion that the radiographic appearances in cases of silicosis afford the most reliable *single* piece of evidence in establishing the existence and the actual stage of the disease in any particular case, in determining the presence or absence of tuberculosis, and in differentiating cases of early silicosis from cases of commencing tuberculosis. . . . . A *complete* opinion in any individual case must, however, be always based both on the radiographic appearances and on clinical examination." In similar tone the Annual Report of the Miners' Phthisis Bureau (172) for 1920 stated: "It is the unanimous opinion of the bureau that a technically satisfactory radiogram is of paramount importance in assisting in the formation of a just decision as to the presence or absence of silicosis. It is also of the greatest utility in the diagnosis of all but the very earliest cases of tuberculosis. Our experience has, however, confirmed the suspicion that unless the x-ray negative reaches a well-defined standard of technical excellence its interpretation may be erroneous." Watkins-Pitchford, (219) whose extensive experience enables him to speak authoritatively, has said that "a technically satisfactory radiograph" is essential to the diagnosis of this condition. According to Pancoast and Pendergrass (151), who have brought out an excellent book on the radiology of the disease, a technically satisfactory plate must be one which, among other things, is taken with a short exposure so as to avoid blurring from cardiac vibration.

Although the x-ray plate is very characteristic and constant, not everything which looks like pneumonoconiosis in the plate is necessarily that disease, however. By x-ray alone, for instance, it is almost impossible to distinguish between pneumonoconiosis and miliary tuberculosis. Such a case was reported recently by Green (69). Very recently Clark (30) has reported having found radiological appearances similar to those of first-stage silicosis in nondusted people with chronic bronchitis and the pulmonary changes incident to advancing years. It has also recently been reported by Collis and Gilchrist (37) that the "snowstorm" radiograph has been found in coal handlers ("trimmers") who have doubtless been around but little, if any, silica dust. They recommended caution in assuming that this type of plate is absolutely diagnostic of silicotic fibrosis.

Before entering into a discussion of the roentgenological changes that appear in this disease, we should recall for a moment what the "normal" chest looks like roentgenologically. This has been well shown by a committee of the National Tuberculosis Association (8). This committee suggested a convenient division of the plate into three vertical zones. The inner one comprises the rootshadows and thus the situation of the tracheobronchial lymph nodes. The middle zone includes the trunk shadows which gradually become smaller as their finer subdivisions are reached. The outer zone embraces the continuation of these smaller trunks until they fade out and disappear peripherally. It is the opinion of this committee (1) that shadows in the inner zone can be disregarded in so far as their clinical significance is concerned unless they be solid or dense and homogeneous; (2) that trunk shadows in the middle or peripheral zones which do not become progressively smaller and disappear are to be regarded as indicating pathological change. The committee's second report (149) represents a particularly clear description of the x-ray of the normal adult's chest.

From the roentgenological standpoint, pneumonoconiosis has been classified variously. Watt, Irvine, Johnson and Steuart (225) employed the clinical classification in use on the Rand at that time and interpreted the plates as representing early, medium, and advanced silicosis. In their judgment in early silicosis, the normally transparent areas between the main trunks "and in the peripheral zone of the lung, are occupied by numerous finer, linear, reticulated or branching shadows," which are due to the formation of new fibrous tissue. This is generalized and bilateral but is sometimes more developed on the right side. There is also slight increase in density of the hilar and root shadows. In medium silicosis, there is a generalized mottling, with "beading" and general increase in intensity of the finer shadows seen in earlier stages, and definite accentuation of the hilar shadows. In advanced stages of the disease, there is a generalized, nodular fibrosis characterized by the fact that "the total area of both lungs is occupied by a large number of discrete, or practically discrete, well-defined, small rounded shadows."

The authors from the Rand reported that asymmetry in a pneumonoconiotic lung is an important characteristic of tuberculosis; that the vertical or "drop" heart, although also found in conditions of asthenia, is very noticeable in tuberculosis. The areas of consolidation (tuberculo-silicosis) frequently appear as sharply defined shadows, while a spreading tuberculosis may throw a ramifying shadow simulating that of early silicosis or a mottling similar to that of medium silicosis. Extensive tuberculosis may so overcast the plate as to obscure the roentgenological evidence of silicosis. Cavities are frequently present in cases in which the silicosis is complicated by tuberculosis. These writers also interpolated the observation that emphysema may obscure the shadows which a silicotic chest would otherwise show.

Childs (113), who worked in close association with Lanza in a study of zinc miners, arbitrarily divided pneumonoconiosis into three stages. These stages in uncomplicated pneumonoconiosis, are as follows:

First stage: Increased density and width of the trunk and hilar shadows, in the latter of which are still dense shadows of nodular deposits; punctate shadows of varying size along the bronchi; no displacement of trachea or heart and no difference in the level of the diaphragm; changes are essentially bilateral.

Second stage: In addition to signs indicative of the first stage, widespread, symmetrical, circumscribed areas of density appear which may increase in size and become more numerous in the lower part of the upper third of the pulmonary field; no signs of cavity, dome of diaphragm is accentuated.

Third stage: Grows out of second stage and has increased number and a more massive grouping of dense shadows often leaving no normal markings in the field; heart is in normal position and the diaphragm very high; narrowing of interspaces, especially in mid-region (vertically).

When tuberculosis has complicated the disease, the several stages present, in addition to the description already given, the following:

First stage: The shadows cast in this stage resemble tuberculosis a good deal, except for its distribution. When tuberculosis develops, apical "stippling" is usually present, healed foci are in evidence, the density is not symmetrical, patches of thickened pleura and moderate displacement of heart and trachea are present.

Second stage: Again asymmetry is conspicuous; mediastinum and trachea are displaced, and cavitation is frequent, limitation of diaphragmatic movement is obvious.

Third stage: Cavitation, marked mediastinal and tracheal displacement, marked fixation of the diaphragm and usually some reduction in the size of the heart are readily detectable.

With the more recent clinical classification, ante-primary, primary, and secondary have also been carried over to the roentgenological field and only these terms are in use in South Africa at present.

According to Pancoast and Pendergrass (151) who have subscribed to the three-stage classification of Childs, an important observation sometimes made in the early stages, is a restriction of the inner half of the diaphragm as though it were held up "by the portionof the lung containing the most prominent trunk shadows." They thought that this might be taken as a sign of beginning functional disability, even before there is clinical evidence that such may be the case. However, they warned against interpreting the early roentgenological signs uncritically, for such signs may be simulated by chronic passive congestion, acute and chronic respiratory infections, bronchitis, irritation from certain gases and, less commonly, malignant growths.

They pointed out that, in the second stage with small dense nodules of fibrous tissue, the distribution is not symmetrical but definitely more developed in the vicinity of the root on the right side. After the mottling becomes generalized, the asymmetry is lost. There is some difference in the density and sharpness of outline of the shadows depending upon the type of dust (same authors). These are densest and most clearly outlined in metal grinders; probably because the fibrosis develops rapidly in response to the stone dust. In coal miners in whom fibrosis is slow in coming on, these pathological structures are less dense, and in cement and asbestos workers, still less so. Pancoast and Pendergrass noted that, as the peripheral lung field becomes more involved, there is a tendency for the more central areas to remain stationary or even to clear somewhat. They raised the question as to whether, by virtue of pneumonoconiotic involvement of the peripheral lymphatics, lymph flow might become virtually suspended and the central portions of the lung tend to clear by the elimination of many of the dust cells (not the fibrosis). The x-ray appearance of the second stage is characteristic and not likely to offer differential diagnostic difficulties. The detection of a super-added tuberculosis in this stage, however, is not always easy. It is very helpful to remember in this connection that the pneumonoconiosis rarely affects the extreme apices as tuberculosis does.

In their description of the appearance of the plate in third stage cases Pancoast and Pendergrass emphasized the fact that the diffuse fibrosis characteristic of this stage may have the appearance of any or all of three stages: namely, (1) fairly frequent occurrence of very large, irregular masses with more or less haze between them; (2) a more frequent occurrence of diffuse fibrosis with rather definite nodules and in general resembling extensive pulmonary tuberculosis; (3) extensive area of consolidation, sometimes more than one, subapical, with dense fibrous bands extending especially forward. These in many cases represent the reaction to both pneumonoconiosis and tuberculosis, for it is known that once the lungs are reacting to dust, tuberculous infection produces a great enhancement of the fibrous process.

V. PROGNOSIS

It is generally conceded that pneumonoconiosis has a very marked tendency to progress irrespective of treatment, although numerous writers have felt that removal from the dusty surroundings may, in the very early stages, arrest the process or even cause its subsidence. According to Jarvis (95) many cases in moderate stages do well and functionally recover, and some of the advanced cases may temporarily improve. On the other hand a most interesting observation was made by Watkins-Pitchford (223) on miners who had been away from the mines during the recent war. Numerous miners, leaving the Rand for military service without demonstrable clinical or roentgenological evidence of silicosis, returned with distinct roentgenological signs of this affection. He thought that this change could be attributed either to (1) the natural progression of disease already started but not clinically detectable, or (2) a very slight degree of pneumonoconiosis hastened in its progress by the development of tuberculosis.

The progressive nature of the affection is greatly enhanced by the presence of tuberculosis; as the following data from South Africa reveal (175). To every 1,000 deaths of cases beginning as simple silicosis, 170 deaths have occurred from other causes; to every 1,000 deaths from tuberculosis alone and with silicosis, there have been 25 and 19 deaths respectively from other causes. "By the end of the seventh year, 29 per cent of cases originating as simple silicosis; 46 per cent of cases of simple tuberculosis; 86 per cent of cases of tuberculo-silicosis; and 89 per cent of cases of silico-tuberculosis have died of their disease."

It is because of the serious prognosis in this disease that prophylaxis is of such great importance.

VI. RELATIONSHIP BETWEEN TUBERCULOSIS AND PNEUMONOCONIOSIS

The data on which is based the evidence of tuberculosis as a complication of pneumonoconiosis are often unreliable. The possibility of exposure to tuberculosis at home or in some other place away from the dusty occupation is usually overlooked. In addition, diagnostic criteria are frequently inadequate. As Landis (111) remarked: "For most part the data . . . . is obtained in one of two ways; First, the number of deaths occurring in a certain industry is taken as an index as to the harmfulness of the particular employment, and as a result of this, many occupations have received a bad name, when as a matter of fact, there was nothing in the industry itself to warrant such a deduction. Second, most of the surveys that have been made have followed the plan of making medical examinations of groups of workers, tabulating the defects found, and then assuming that, if there was a high percentage of certain abnormalities, these abnormalities were to be charged against the occupation." He has pointed out what is obviously an important fact that *many people who have died from pure, uncomplicated pneumonoconiosis have been diagnosed tuberculosis.* This fact, among others, has rendered much of the literature on the subject open to serious criticism. Before a diagnosis of tuberculosis is arrived at in people with pneumonoconiosis, abundant clinical evidence should be at hand and numerous examinations of the sputum for tubercle bacilli should be made.

Validity of data

Two important considerations should be taken into account in a discussion of the relationship: These are (1) How much simple pneumonoconiosis is reported as phthisis or tuberculosis and (2) If the tuberculosis is truly tuberculosis, what of the proportional ratio of tuberculosis in pneumonoconiosis to tuberculosis in other industries comparable from the standpoint of hygiene, wage level, education, etc: on the first point a fair amount of data is available; on the second much information is to be desired.

There are several criteria by which data on the relation existing between these two diseases may be evaluated. In the first place, as one looks over the literature, especially that containing statistical data, one is impressed with the fact that pneumonoconiosis as such is rarely mentioned as a cause of death. Table after table of mortality rates contain figures on tuberculosis and on the nontuberculous respiratory diseases (bronchitis, pneumonia, and *other* diseases), but rarely on pneumonoconiosis as such. The literature from South Africa is an exception. This causes one to question whether the differential diagnosis between tuberculosis and pneumonoconiosis has not been uncritically made with the result that most pulmonary diseases among miners which are not bronchitis, pneumonia, asthma or other rarer but recognizable disease entities, are lumped under the head of tuberculosis.

In the second place numerous authors have wittingly used the word tuberculosis as an inclusive term, because there seemed no other way out of the maze of data contained in death certificates. For instance, Drury (50) stated that all the "death certificates (in his statistical study) were first classified by cause, those giving as cause of death pulmonary and other forms of tuberculosis being subjected to intensive analysis. *The term 'pulmonary tuberculosis' has been used to cover all fibroid conditions of the lungs resulting from the inhalation of particles of iron and sandstone, with the tuberculous infection which generally, sooner or later, becomes superimposed on the former condition* (*italics mine*). In the records for the past twenty years the two conditions are inseparable, as one notes under heading 'Cause of Death' on the original death certificates, that a great variety of terms are used, e.g, tuberculosis, pulmonary tuberculosis, chronic fibroid tuberculosis, grinder's consumption, tuberculosis and grinder's consumption, pneumonoconiosis, tuberculosis and pneumonoconiosis, etc. Therefore, any attempt to separate tuberculosis from pneumonoconiosis, as recorded, would result in inaccuracy." His are the data that give a death rate from tuberculosis of 1900 per 100,000 among grinders and polishers in an ax factory, as compared with 160 per 100,000 among other workers in the mill. What the data show with remarkable clearness is that the occupation of grinding and polishing in an ax factory is an exceedingly hazardous occupation because it leads to an astounding proportion of deaths from pulmonary disease. Such data, while perfectly good from certain standpoints, serve only to cloud still further the question of incidence-relationships between the two affections,—tuberculosis and pneumonoconiosis. Complications such as these probably will inhere in our data until better differential diagnostic methods are practiced.

In the third place there should be further appreciation of the distinction between ratios and rates. As Greenburg (71) has pointed out, ratios "depend on two independent variables, and a high ratio of tuberculosis deaths to total deaths may be produced by a low mortality from other causes as well as by a high mortality from tuberculosis." Such a fact, while obvious, is frequently lost sight of in considering the several aspects of this problem.

Numerous writers have held, as has Landis, that simple pneumonoconiosis is the cause of death of a large majority of people among this class of workmen. They have based the contention on (1) the absence of an unusually high tuberculosis death rate among families of these workers; (2) the low death rate among miners under 25 years of age (Cobbett (32)), indicating a low incidence of infection in the homes from which these young men come; and (3) the fact that "causes of death are seriously vitiated by the popular nosology, which assigns the majority of deaths of miners to consumption" (Arlidge (5)). Others have mentioned as factors the low degree of infectivity of the superimposed tuberculosis which gives off very few tubercle bacilli. And Collis (33) intimated that although tuberculosis is a common complication, the bacilli are less virulent. To this Cobbett answered that the presence of fewer bacilli than in ordinary pulmonary tuberculosis would explain the relative infrequency of familial tuberculosis among these workers.

Most writers, however, have assumed that tuberculosis is the cause of death in a very large number of this class of workers. They have arrived at this deduction (1) from the fact that there is a much higher incidence of pulmonary disease among them than among the general population, and (2) on the incidence of tubercle bacilli in the sputum. Ritchie (178) for instance found tubercle bacilli in the sputum of 17 out of 23 Cornish miners suffering from phthisis, and Baldwin (9), as will be shown later, obtained similar results in a very large percentage of granite workers.

In this section an effort will be made to analyze some of the factors in the relationship between these two affections and to present certain data in respect to the coincidence of the two diseases in several different dusty industries.

Incidence

From the latter part of the sixteenth century it has been stated innumerable times that miners and other workers in dust are very likely to die consumptive. Many of the diagnoses of consumption which were made before the day of modern exploration of the chest were faulty and undoubtedly many people who died of uncomplicated pneumonoconiosis were diagnosed as consumption. Many reports that have appeared during recent decades show with remarkable clearness that critique is still wanting in this direction. But despite this fact, it has been clearly shown over and over again that the proportion of tuberculosis in workers who have breathed siliceous dusts for a long time remains high even when much faulty diagnosis is discounted. The committee on the health of Cornish miners in its report for 1904 (170) concluded that "it seems enough that the stone dust which the Cornish miners inhale produces permanent injury to the lungs . . . . and that this injury, while it is apparently capable of gradually producing by itself great impairment of the respiratory function, and indirectly of the general health, also predisposes enormously to tuberculosis of the lungs, so that a large proportion of miners die from tubercular phthisis." In the general tenor of this quotation Wheatley (227), Oliver (145), and many others have agreed. It is the opinion of Cobbett (32), who has briefly discussed this problem, that it remains an open question in how far tuberculosis modifies the excessive mortality among dust breathers. To him it is plain that pneumonoconiosis leads directly to death in many cases and that when tuberculosis does complicate the picture, as it often does, tubercle bacilli are scanty.

The very careful clinical and radiological work and the careful sputum examinations and autopsies that have been done so well and for so many years by the Miners' Phthisis Prevention Bureau of South Africa and the detailed study of the Barre, Vermont, granite cutters which was reported by Baldwin (9) are two conspicuous pieces of work which force the conclusion that tuberculosis occurs with very great frequency in people with silicosis, albeit many silicotics die without tuberculosis.

Such data as that of Barwise (11) in 1913 arrest the attention. He showed that the death rate from tuberculosis among gritstone workers "is 20 times greater than in the same social class employed in agriculture, and 17 times greater than in other workers."[13] Smith (195) encountered an extraordinary incidence of death from tuberculosis in Australian miners with silicosis and reported that such miners "were 23 times as susceptible to tuberculosis" as nonsilicotic persons (151). The Transvaal Mining Regulations Commission in 1910 (209) reported that the ratio of deaths from tuberculosis among "white mine employees as compared with those from that cause amongst nonmining adult males was approximately as 6.3 to 1." Jarvis (95) has observed tuberculosis as the cause of death in more than 80 per cent of the deaths of the granite cutters of Barre, Vermont, and Collis (34) reported that of ganister workers who die, tuberculosis is the cause in more than three-fourths of the cases.[14]

Age at which tuberculosis supervenes

A very striking feature of this relationship and one commented upon by many observers is that tuberculosis as a complication comes at a comparatively late period in life. If the mortality from tuberculosis among workers exposed to siliceous dust is compared with the mortality from tuberculosis among those not so exposed, it is found that those dying in the silica group have their highest incidence later in life than is the case with ordinary pulmonary tuberculosis, the highest incidence being above 45 and usually above 50 years of age. This corresponds closely to the highest incidence from tuberculosis among coal miners. The maximal mortality in the region covered by the Transvaal Commission Report (208) occurred at 30 to 35 years in the nonmining males as compared with a maximum at 35 to 40 among the miners. A similar observation is contained in the Royal Commission on Metalliferous Mines and Quarries (181) which lays down the following statement: "If in any given class a high death rate from pulmonary tuberculosis is found, occurring at a later period of life than is usual for pulmonary tuberculosis, and if this high death rate is associated with a high death rate from other respiratory diseases, then this class is exposed to the inhalation of injurious dust." In this connection, too, the recent work of Collis (36) is germane. He has pointed out that the frequent association of the two diseases is of statistical importance because many cases of death are erroneously reported as tuberculosis; some of these are due to simple silicosis and many more are due to tuberculosis and silicosis—the so-called tuberculo-silicosis. He further related that people dying in the silica group have their highest incidence later in life than is the case with those dying of ordinary pulmonary tuberculosis, the highest incidence being between 55 and 64. Ickert (94) noted a very high incidence of tuberculosis among copper and slate miners, who also died later in life—many in the sixth decade. And McFarland (120) pointed out that the amount of tuberculosis is low in families of granite cutters, probably because the cutter develops his tuberculosis at a later age than the average, which lessens the opportunities for infecting the children of the homes at an early age.

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[13] It is true, however, that this report of Barwise is based upon death reports and is, therefore, wholly open to criticism.

[14] Both these statements are based upon mortality statistics.

Does this late age of death indicate that people with pneumonoconiosis and tuberculosis do not *develop* their disease until comparatively late in life? Can it be that tubercle bacilli are taken into these persons at the usual or average age but that they are held by the scar and fibrous tissue and not allowed to spread over the lung? It is a fact, as shown by Gardner (62), that when both pneumonoconiosis and tuberculosis coëxist in experimental animals, there is a fibrous reaction greater than might be expected from simply a summation of reactions to both affections separately. Is it likely that an added amount of scar would contribute unusually effectively toward localizing the infection and preventing its spread? One cannot answer these questions definitely. However, it seems unlikely that this group of persons, who live among their associates in a normal way when not underground, would be peculiarly exposed to tubercle bacilli later in life than others in their social group. There is some plausibility to the matter raised in the second question: namely, the hampering effect of the fibrosis upon bacillary spread. Haythorn (80), Beattie (12), and others have contended that fibrosis should be regarded as protective in tuberculosis in the sense that it *prevents the spread* of the disease. But the converse is equally true: namely, that the fibrosis which would thus focalize and hold tubercle bacilli because of interference with the lymph drainage incident to scarring, would lead to a *larger number of foci and possibly larger* foci in the lung although a *less extensive spread* might be present. And this is what is frequently observed, especially roentgenologically, in tuberculo-silicosis. However, massive tuberculous or tuberculo-silicotic lesions often undergo a rapidly progressive, down-hill course once clear-cut symptoms become established.

Time relationships

That certain dusts produce a deleterious effect upon the lungs in a comparatively short time and that certain other dusts produce their effect so slowly that the changes are relatively inappreciable for years, is well recognized and has already been mentioned. For instance, a serious grade of silicosis *may* develop after three years of exposure under particular conditions while at the end of 30 years in some of the dusty trades (e.g., coal mining) the miner may show comparatively little pulmonary change. It must be obvious that the duration of exposure before the onset of tuberculosis, as well as the type of dust, might be a material contributory factor in the development of the latter disease. In order for pneumonoconiosis to predispose to tuberculosis we must suppose that the underlying condition of pneumonoconiosis must itself be more or less well developed. If tuberculosis appears within the first few months of the workman's exposure to siliceous dust or within the early years of his contact with the dusts that work more slowly, the chances are good that pneumonoconiosis would have had little or nothing to do with the engrafting of the infectious disease. Many writers, in failing to take this into account, have added to the difficulties in the way of a clear understanding of this problem. This is well illustrated and emphasized by Landis (111) in the study of tuberculosis among potters.

If a miner develops simple silicosis in the mines of the Rand, the shortest period in which he does so is about four and a quarter years, but for all who contract the affection, the average period is about 10 and a quarter years and this is becoming increasingly longer (223). Only about three per cent of the total working miners and only about seven per cent of all those employed for 10 or more years annually become silicotic.

Sanitation of environment

Numerous authors have reported it to be their belief that pneumonoconiosis as such, is not the sole contributory factor which is responsible for the high incidence of tuberculosis among workers in dust. Among the more recent writers Landis (110), for example, believed that the general economic and hygienic surroundings in which workers live and work have a distinct bearing upon their liability to infectious disease. Lanza (113) reported a great deal of tuberculosis in the sordid and very bad hygienic surroundings of the homes of the zinc workers he investigated. And McFarland (120) indicated that the relative freedom from tuberculosis in the families of granite cutters when the cutters themselves had so much of it was due in part at least to the fact that the cutter is above the average in intelligence, makes good wages, and provides well for his family: this, in addition to the fact that the cutters develop their tuberculosis too late in life to infect the family when the children are small. Watkins-Pitchford (221) believed that the general unsanitary conditions of the mines, the absence in them of such disinfecting agents as light and dryness, and the fact that the miners eat one meal a day underground with unwashed hands would account for a great deal of tuberculosis among them. This author discovered the fact that many tubercle bacilli were present in the mines, where opportunities were unusually good for infection. Upon examining 250 specimens of expectoration taken at random from the floor inside the mines, he (222) found that 15.2 per cent contained tubercle bacilli; while only 2.5 per cent of 120 specimens from the surface outside the mines contained tubercle bacilli. In his opinion (221) tubercle bacilli are present in a very high percentage of silicotic lungs in the late stages of the disease where they may in many instances be saprophytic, even though the silicotic lung is in all stages more susceptible than the normal lung to tuberculosis.

In certain dusty occupations, such as coal mining, the miner appears to have even less tuberculosis than his family. In others, the workmen's incidence of death from tuberculosis is far in excess of that of his family. The opportunities which a workman in dust has to contract tuberculosis from his environment should always be considered. The presence of tuberculosis in his immediate family might lead to tuberculosis in the miner just as it might lead to the same disease in his brother who had never been exposed to dust. Such factors complicate the question a good deal and must be taken into account if data on the interrelation between pneumonoconiosis and tuberculosis is to be clearly understood (111).

What constitutes a dusty atmosphere is a relative matter. Different parts of shop or mine at different times of the day vary tremendously in the amount of dust present, depending upon the type of operation, the adequacy of ventilation, etc. According to Higgins, Lanza, Laney and Rice (85) the variation in "dustiness" of the atmosphere of the same mine on the same day in the Joplin district ranged from two to 200 per cent of a given norm.

Occupations involved

It is one of the characteristic features of many reports on the subject that the type of dust inhaled contributes materially to the incidence of superadded tuberculosis. In fact, it is one of the few points on which the large majority of authors agree. Probably the simplest way to present this fact will be to give data on the situation with respect to the two diseases in several of the more important dusty occupations.

1. Mining. a. Hard rock mining. There are many kinds of mining and many substances mined. Among the latter are coal, cobalt, gold, lead, zinc, copper, nickel, slate, iron, and silver. In obtaining these various substances, miners are exposed to much or little dust depending upon the specific process involved; whether drilling, loading or hauling ore, whether machine drilling is employed, whether the process is a wet or a dry one; how efficient the ventilation is, what the hours of work are, what the hours are at which blasting is done, etc. They are exposed to injurious or bland dusts depending upon the nature of the ore mined, and especially upon the geological environment of the ore and the composition of the rock in the immediate vicinity.

These substances are found chiefly or solely in strata containing much hard rock. This is especially true of gold, lead, zinc, copper, cobalt, iron, and nickel and these have been grouped conveniently by Pancoast and Pendergrass (151) under the heading of hard rock mining. The occupations are hazardous not because of the damage the dusts of any of the several specific substances may cause when inhaled, but because of the effects derivable from inhalation of silica dust that is created in the process of the mining. Such damage develops rapidly or slowly depending upon the percentage of free silica and the amount and availability (degree of fineness, dryness, etc.,) of the siliceous particles.

However, an exception to this statement may certainly be taken in respect to iron. Zenker's original case (238) was one of siderosis. Recently Cronin (44) has reported pulmonary fibrosis in hematite miners. Of the miners examined by him, however, many had no symptoms, some having worked for thirty years. Analysis of the dust showed 12 to 14 per cent of silica and 55 per cent of iron. The silica probably had much to do with the pathology and symptoms. Whether the inhalation of copper ore as such leads to pneumonoconiosis is moot. That copper workers are exposed to siliceous dusts is certain and that they develop chalicosis and tuberculosis with great frequency has often been reported (although autopsies are exceedingly uncommonly performed (Hoffman (88)). It has been pointed out by Brinkmann (21) that people having chalicosis and tuberculosis die at a later age (years 40 to 50) than people having uncomplicated tuberculosis. It is the burden of many writers to indicate that such miners are often the victims of superadded tuberculosis: in the South African and Australian gold mines (Miners' Phthisis Prevention Committee (66), Purdy (163), Kerr (100), Smith (195)), in the zinc mines of Missouri (Lanza (113)) and in the copper mines of Germany (Ickert (94)).

It has been the experience in the South African gold mines that among the native laborers employed, the evidence of simple tuberculosis (1923) was three and one-half times as great as that among the European workers in these mines, while simple (uncomplicated) silicosis was 56 times as great among the latter as among the former. The relative rarity of simple silicosis among the native laborers arises from the prevailing shortness of employment (Watkins-Pitchford (223)).

Tunneling through rock brings workmen into siliceous dusts. It is not generally known that there are approximately 2,000 men employed underground in New York City as drillers, excavators, blasters, etc., and that contracts have been let which will require the labor of 5,000 men in this kind of work for six years. The type of rock in New York and vicinity varies a good deal and contains total silica in a proportion of from 56 to 95 per cent and free silica from less than one to 84 per cent. A good percentage of the men had worked less than 10 years and with many of them employment has been intermittent. Yet 57 per cent of 208 of these workmen were found to have detectable evidence of silicosis, and six of them had active tuberculosis. Two of the latter, however, were nonsilicotic individuals. These data were reported by Smith, Fehnel and a joint silicotic committee (194).

b. Coal mining. Coal miners as a class are not susceptible to either pneumonoconiosis or to tuberculosis, and when pneumonoconiosis does develop in such persons it is said to be due to the siliceous dust which is derived from the rock of the mines rather than to the coal dust itself. However, coal miners may develop pneumonoconiosis which eventually becomes lethal without the intervention of tuberculosis or other infection. This is an important consideration which should not be overlooked. The incidence of pneumonoconiosis has increased since the advent of machine drills for cutting through rock or earth "faults" which lie between or alongside the seams of coal. This has been especially true in some of the bituminous mines in England (Tattersall (200)) in which the "hard ground faults and headings" show considerable amounts of silica. Tattersall studied 22 cases who showed signs and symptoms of pneumonoconiosis; of these, 16 had roentgenological evidence of tuberculosis, and six presented clinical evidence of this complication. The pneumonoconiosis in coal miners is slower in development than that in hard rock miners but clinically and roentgenologically it is not different from the latter.

Although it is assumed that the damage to coal miners' lungs is derived from siliceous dust, it is a fact that hard coal miners develop a good deal more pneumonoconiosis, especially second and third stages, than do soft coal miners. Whether there is more silica associated with the hard coal formations than the soft, I do not know. Very recently Jousset (98) has contended that coal miners' lungs usually contain a considerable proportion of silica and iron which are responsible for the fibrosis when the latter develops.

Several intimations of the relative infrequence of tuberculosis in coal miners have already been given. Indeed it is so infrequent that many writers have postulated the existence of some bactericidal or protective element in coal dust (Hirt (87), Landis (110), Wainwright and Nichols (218), Shufflebotham (190) and many others). Regarding the relative incidence of tuberculosis in several different categories of miners in Great Britain, Shufflebotham (190) has said: "Tuberculosis of the lungs is not commonly found among coal miners as among many other occupations, and the statistics of the registrar general with regard to mortality from this cause show that while the mortality figure for all occupied males in England and Wales is 175, that for the coal miner is only 85; metalliferous miners, however, are not so fortunate in this respect, the figure for the Cornish tin miner being 838 (the highest on the list of all occupations); the copper miner, 501; and the lead miners, 344."

The low death rate from tuberculosis among coal miners is particularly interesting because of the fact that such miners frequently die of nontuberculous pulmonary diseases such as asthma, bronchitis, or pneumonia, just as do other miners. This question is discussed in considerable detail by Hoffman (88). So coal mining is not a particularly healthy occupation, although Barwise (11) has reported a death rate from all causes of 9.2 per 1,000 among coal miners as compared with 14.6 for "others." In 1858 J.B. Thomson (205) gave the duration of life among coal miners at 26.1 years and that of undefined laborers as 34.0 years.

2. Quarrying. Quarrying embraces a large number of occupations such as drilling, blasting, crushing, and hauling a large variety of rock, some of which are dangerous and some innocuous. Among these types are sedimentary stone and igneous stone, the former being more dusty and the latter (comprising granite) being exceedingly hard. Quarrying also includes working in the bottom of pits where dust and dampness are both abundant and working in the open air at the top of pits where the concentration of dust is relatively low.

In the consideration of the complication of tuberculosis among quarrymen, *granite* workers come up first for attention. It has been recently shown by McFarland (120) that the air in granite cutting plants of Barre, Vermont may contain as many as 2,300 particles of dust per cubic centimeter and that the worker inhales approximately 2,000,000 particles of dust with each breath. He further stated that Barre granite contains about 70 per cent silica and 25 per cent *free* silica. Among this class of workmen the death rate from tuberculosis which has always been rather high, jumped to an alarming level at the time machine drilling became widespread. According to Hoffman (90) the death rate from tuberculosis among granite quarrymen in the New England States was 432.0 per 100,000 during the years from 1895 to 1899 and 1056.7 during the period from 1915 to 1918,[15] and this in face of the fact that among the general population the rate was steadily declining in the intervening years between these two periods. He felt that "the effect of dust inhalation is one of growing seriousness according to the rate of dust accumulation in the lungs." Jarvis (95) has shown that pneumonoconiosis begins to develop fairly soon after employment is assumed; that the average development of first stage findings is from 10 to 20 years; of second stage findings from 20 to 40 years; and of third stage findings from 30 to 40 years. As in the case of certain miners, so in granite workers tuberculosis makes its appearance during the comparatively late years of life. Again the question arises as to the correctness of the diagnosis in many of these cases. Unfortunately it is impossible to know whether many of the deaths reputed to have been due to tuberculosis were not in reality due simply to uncomplicated pneumonoconiosis. For autopsies in such circumstances have been exceedingly few and sputum examinations have been too scatteringly done. However, Baldwin (9) has given excellent evidence of the high incidence of tuberculosis in the granite workers in Vermont. His committee examined more than 1,000 cutters of Barre, 427 of which were examined in detail and reported statistically. Of the 427 men only 28 had no signs of silicosis; nearly all who had worked as long as 10 years had considerable silicosis and about one-fourth of the number had either definite or suspected tuberculosis; the majority of these were still vigorous and at work; of 56 cases of suspected tuberculosis (by x-ray), 27 showed physical signs of the disease. Twenty-six cases had tubercle bacilli in the sputum. He thus pointed out that a careful physical examination, a satisfactory roentgenogram and patient, painstaking sputum examination will usually detect the presence of tuberculosis associated with pneumonoconiosis.

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[15] These rates are based on death certificates and are therefore not to be taken at their face value. Undoubtedly a good number of these deaths were due to pneumonoconiosis alone and some of them to undefined pulmonary disease.

Granite dust is essentially silica dust and, like the latter, is insoluble and is readily carried to lymph nodes in the lungs where it leads to marked fibrosis. Gardner (64) has shown that guinea pigs exposed to prolonged inhalation of granite (and other) dusts become definitely more susceptible to tuberculosis.

In addition to granite, other stone such as *limestone* and *marble*, are quarried. It is notable that there is very little pneumonoconiosis, among limestone and marble workers and not more tuberculosis than among the general population. The amount of silica in limestone is slightly more than one per cent and in marble it is practically nonexistent. Gardner (64) has pointed out the fact that marble dust is largely soluble and that, although after prolonged inhalation of marble dust, a certain amount of insoluble siliceous matter accumulates in the lung, calcium is not found there and marble dust produces no essential reaction in the tissues.

3. Metal grinding. In tool and implement making the grindstone is greatly used and is the major source, possibly the only source, of the dust which frequently does the grinder harm. That iron or other metalliferous dusts are somewhat harmful *per se* is probable, but it is established that the silica from the grindstone may lead relatively rapidly to the development of silicosis. Pancoast and Pendergrass (151) reported having examined 25 grinders of whom a large majority were in the first and second stages. In some of these the affection developed early.

It is notorious, especially in the older literature, that the mortality from so-called *grinder's rot* (presumed to be tuberculosis) was extraordinarily high. Prior to 1800 there was considerable diversification and no specialization in the cutler's occupation. In 1822 Knight (105) commented upon the fact that grinder's rot had become common only recently because, until a few years earlier, workmen had not been exposed continuously or for considerable periods to great amounts of dust such as those would be who kept constantly at the grinding wheels. Recently Drury (50) has reported the astounding death rate from tuberculosis of 1900 per 100,000 among grinders and polishers in an ax factory as compared with a rate of 160 per 100,000 for other employees in the mill. But Drury in the circumstance had to depend (1) simply upon the death certificate which must certainly be regarded with suspicion in a large number of instances; and (2) upon the fact that the polishers and grinders were nearly all foreigners which has also been thought to make a good deal of difference. This is of no importance as bearing upon the race, but it may be of considerable importance in respect to the sanitation in the home, the amount of drunkenness, the wages, the amount of food, all of which factors bear definitely upon the incidence of tuberculosis. How many of the deaths recorded as due to tuberculosis were actually due to simple pneumonoconiosis can never be determined even though recourse be had to the original certificates as Drury has carefully done. Such data as he presented certainly prove beyond peradventure that the occupation of ax grinding and polishing is often an exceedingly grave hazard to life and health. The fact that careful and special clinical, roentgenological, and laboratory investigation has many times proved that tuberculosis is exceedingly prevalent among this class of workmen is, however, good collateral evidence that many of Drury's deaths were from this disease. The further fact that in Drury's report the incidence of "other" pulmonary diseases among polishers and grinders was unusually high leads to the presumption of a high incidence of tuberculosis which is the chief pulmonary disease (50). There is no mention whatsoever of pneumonoconiosis as a cause of death.

4. Pottery making. "Potters have long been known as a group of workers in whom incapacitating lung conditions are prone to develop in time and have been regarded as more or less subject to tuberculosis" (151). Potters work in clay which contains varying amounts of free silica that is available for inhalation especially from the dust created by broken fragments and dry clay in the kilns and sheds. The larger number of the processes are carried out with wet clay. Such workers apparently get but small amounts of silica (10 to 25 per cent in some of the English potters, Nicholson (143)) with the consequence that the pneumonoconiosis which they eventually develop comes on very slowly and usually shows itself clinically only after many (20 to 40) years (Pancoast and Pendergrass (151), Landis (111)). When signs and symptoms of pneumonoconiosis do ensue, they resemble those of pneumonoconiosis induced by other types of silica or rock dust. Such workmen are rather subject to tuberculosis, but Landis considered the trade a good health risk. However, he felt that many potters eventually die of uncomplicated pneumonoconiosis. He insisted upon the value of repeated examinations of the sputum in the differentiation between simple pneumonoconiosis and pneumonoconiosis with pulmonary tuberculosis superadded. The roentgenological aspect of this question and indeed of several of the most important dusty occupations has been very clearly dealt with by Pancoast and Pendergrass (151).

5. Brick making. There is reason to presuppose that brick makers have substantially the same experience in respect to pneumonoconiosis as do potters for both groups handle dried earth and clay in which there is usually considerable sand. But it is certainly uncommon to see signs of pulmonary disorder among makers of ordinary brick. This may be due to the fact that many of the manipulations in brick-making involve the handling of wet material only. Pancoast and Pendergrass have seen no case of pneumonoconiosis among them and reported that one man who had been occupied for 40 years showed no silicotic changes in the lungs. Several writers (Middleton (128), Collis) have reported pneumonoconiosis and tuberculosis among the workers of silica brick.

There is, however, a certain type of brick made of ganister, the manufacture of which is considered a dangerous trade. According to Sutherland (199) a great deal of ganister dust is disengaged in the process of ganister brick manufacture, and the better grades of this product contain from 87 to 96 per cent of silica. The consequence is that the incidence of silicosis is very high among those employed in such works. Of 1,254 such workmen examined by Sutherland, 8.3 per cent were found to have either silicosis, tuberculosis, or both. He found that men employed in different parts of the works varied greatly in the incidence of pulmonary disease. This latter is a matter to which insufficient attention has been paid in the past.

6. Carborundum manufacture. Carborundum is essentially silicon carbide. It contains no free silica. According to Holmes (92) employees in the dusty atmosphere of the carborundum plants at Niagara

Falls escape serious pulmonary disease. But it is his opinion that the dust is harmful and that they escape by virtue of their inconstance which leads to a marked labor turnover. Clark (30), (31) has found no preponderance of pulmonary disease among such workers even those employed for a considerable number of years. Experimentally, Gardner (62) has shown that carborundum dust is harmless to the normal lung. He found, however, that if it is inhaled during a developing pulmonary tuberculosis, there appears a degree of fibrosis greater than could be expected from a "summation" effect of response to both excitants. Exposure of guinea pigs for more than three years to the inhalation of crystolon—and abrasive made up of 98 per cent of silicon carbide and 0.5 per cent of silica produced strikingly little change in the lungs (Willis (229)) and did not predispose to tuberculosis.

7. Glass making. Much of the work in the manufacture and handling of glass is innocuous, while certain of the occupations in the industry are distinctly injurious to health. This latter applies to the mixing operation preliminary to actual manufacture, to cutting, grinding, and blowing. Several of these predispose to tuberculosis (Hoffman (89)). In 1873 Hirt (87) gave the average age at death of glass grinders as 42½ years. In general this hazard has experienced a very material diminution in recent years (Hoffman, (88)). Silica which is one of the basic ingredients of glass is the important, if not the sole, cause of pulmonary damage in this industry (this obviously leaves out of discussion the effect of lead and other substances used in the industry but having nothing to do with pneumonoconiosis).

8. Sand blasting. This process is still carried on within enclosures where the workmen are unprotected from the inhalation of fine, siliceous particles by anything more than a handkerchief tied over the nose and mouth. The concentration of very fine particulate siliceous matter is quite as great in this occupation as in any of the dusty trades. In certain sand blasting operations, strong currents of air are thrown in the direction of the blast itself in an effort to carry the dust away from the operator who stands behind a carbinet during the operation. Thompson (204) has given a good description of sand blasting and has recounted its operative procedures, dangers and the protective efforts employed.

9. Cement making and handling. It is generally stated that cement workers do not develop pulmonary fibrosis from their occupation and are not unusually susceptible to tuberculosis. Nagai[16] (141) exposed some guinea pigs to the inhalation of cement dust and others to inhalation of cement dust to which tubercle bacilli had been added. The dust neither produced any deleterious effect upon the normal lungs nor modified the development of tuberculosis in any way. Yet Pancoast, Miller and Landis (150) examined 20 cement workers, one of whom had been occupied for 19 years, and found definite roentgenological changes of second stage pneumonoconiosis in 15 and possible first stage changes in the remaining five. (See also Pancoast and Pendergrass (151)). It is rather surprising that cement does not lead to more damaging effects in the lungs because, according to Tucker (212), it contains approximately 15 per cent of silica. This author gave the following analysis of the crude mix from which cement is made:

	per cent
Silica	15.18
Iron Alumina oxide	5.06
Calcium carbonate	76.34
Magnesium carbonate	2.90
Undetermined	0.52

Finished cement contains silica in amounts of 22.98 per cent and lime to the extent of 63.10 per cent. The association of other dusts may account for the harmlessness of this product. This industry, like that of carborundum making, is of too recent origin for us to know what the ultimate effect upon the lungs of its workmen will be. Yet it is well established that diseases of every sort, and especially pulmonary diseases, are notably uncommon amongst cement workers.

10. Lime handling. Lime is readily soluble in the tissues. Lime workers are a healthy people in general without higher incidence of any of the pulmonary diseases than people not so employed. Reckzeh (167) has shown that tuberculosis is rare among these people, and Selkirk (186) was unable to find either pneumonoconiosis or tuberculosis among lime workers. He advocated lime and cement working as a prophylactic measure for those predisposed to tuberculosis. Coutière (41) exposed people with pulmonary tuberculosis to the inhalation of lime dust and carbonic anhydrid for five minute periods 10 or 12 times a day continued for two, three, and four months—and reported many of them as having become definitely arrested and others much improved. However, one, might properly take exception to such work on several counts such as the rapidity of recovery, shortness of the period of treatment, definition of the term "arrested," the evaluation of the psychic effect of the treatment, etc. Barwise (11) gave the death rate for lime workers as being lower than that for agricultural workers, and Thackrah (202) in 1831 found no deleterious effects from the inhalation of lime. He observed that "bricklayers and plasterers' laborers, like asses, never die." *Plasterers* appear to be as exempt as other lime workers from serious pulmonary disease.

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[16] Whether dust used was lime or cement is not quite certain from the abstract. Original reference was not available.

11. Asbestos handling. Asbestos is a calcium and magnesium silicate (Cooke (38)) which contains 40 per cent of free silica. It is quarried out of rock which contains a high proportion of silica. In its manufacture into goods, it must go through the processes of carding, spinning and heating,—all of which, according to Oliver (147), are very dusty. The latter author described several cases; in these no tuberculosis was detectable. Pancoast, Miller and Landis (150) found definite roentgenological changes in asbestos workers. Cooke (38) reported a case of asbestosis and tuberculosis in a woman of 33 who had worked 20 years at her trade. There was extensive bilateral pulmonary fibrosis in the x-ray plate in addition to roentgenological evidence of tuberculosis. These findings were verified at autopsy. Wood (236) has given a clinical and radiographical description of this disease which in certain respects differs from ordinary silicosis. For instance he found wasting, cyanosis and frequent clubbing of the fingers in addition to the dyspnea, cough and other symptoms that are characteristic of pneumonoconiosis from other cause. He found that roentgenologically the reaction tended to be located chiefly in the lower two-thirds of the lungs and the shadows were a fine network not so coarse as those in silicosis. He observed that pneumonia and bronchitis were common in such persons, but it remained an open question whether tuberculosis was common among them. He based his report on 15 cases.[17]

A very valuable table of mortality rates from tuberculosis in various dusty trades was compiled for the English journal "Tubercle" (211) in 1922. It is reproduced in table 3. The table carries a rough analysis of the dust in the several occupations listed and pays particular attention to the amount of free silica. It gives the annual death rate and the ratio which the death rate from this cause bears to that from all causes. It is unfortunate that the term phthisis is used, for this term includes both uncomplicated pneumonoconiosis and pneumonoconiosis with tuberculosis.

VII. PROPHYLAXIS AND TREATMENT

It is one of the conspicuous characteristics of pneumonoconiosis that is is usually unremittingly, if slowly, progressive. This is emphasized in the most recent report of the Miners' Phthisis Medical Bureau (175), in which the data show clearly that the disease tends to advance irrespective of whether the miner retires when his disease first becomes manifest or whether he continues at his occupation for months or even years after the diagnosis is made. Therefore, it is much more important to *prevent* the development of this disease than to treat it after it has become clinically established.

Although it is demonstrated that not all people are equally susceptible to the effects of dust, it is patent that workmen would never become pneumonoconiotic if they did not breathe particulate matter into the lungs with the air. And it is logical that protective efforts should concern chiefly this aspect of the problem. Preventive measures have been employed which (1) lessen the amount of dust, chiefly by the use of respirators and masks, by ventilation, sprinkling, regulation of hours for blasting, etc.; those which (2) by initial and periodical physical examination allow only selected people to be exposed and those which (3) have regard to the general hygiene of work places and homes.

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[17] Since this was written Merewether (J. Indust. Hyg., 1930, xii, 198 and 239) has given a very detailed and complete description of all aspects of asbestosis. He concluded that the affection has a set of characteristics which differ considerably from those of silicosis and that the asbestos industry is a distinct hazard to health.

TABLE 3

Tuberculosis statistics. Mortality from pulmonary tuberculosis in various dusty trades

OCCUPATION	COMPOSITION OF DUST		ANNUAL DEATH-RATE PER 1000 LIVING	DEATHS FROM PHTHISIS EXPRESSED AS PERCENTAGE OF DEATHS FROM ALL CAUSES
	Free silica	Other constituents		
Flint knappers (Brandon)	100 per cent		41.0	77.8
Ganister miners (Stockbridge)	95 per cent		22.3	67.8
Sandstone cutters (Germany)	Up to 95 per cent		22.0	
Tin mining (Cornwall)	75 per cent	Tinstone, feldspars and micas	17.6	42.0
Sandstone masons (Grinshill)	Up to 95 per cent		16.7	52.4
Grinders (Sheffield)	50 to 100 per cent	Some oxide of iron	15.0	49.7
Granite cutters (Maine and New Hampshire, U. S. A.)	30 per cent	Feldspars and micas	5.3 (1906–09) 11.1 (1915–18)	47.8
Gold mining (Transvaal)	Gold-bearing quartz, i.e. silica		....	42.1
Gold mining (Bendigo)	Gold-bearing quartz, i.e. silica	Other minerals	12.7	23.5
Granite cutters (Aberdeen)	30 per cent		5.7	38.0
Sandstone masons, getters and dressers (England and Wales, 1910–12)	80 to 90 per cent		5.2	21.1
Lead mining (England and Wales)	Quartz and chert, i.e. silica	Lead ore. Limestone sometimes takes the place of quartz in mother rock	4.5	16.4

Potters	Flint, i.e. silica in certain processes only	(Alumina) China clay	3.1	18.9
Occupied and retired males (15 years and over), 1900–02			2.1	13.1
Brickmakers (England and Wales)		Alumina and silicates	2.1	10.1
Lime and brick burners (Switzerland)		Calcium carbonate and clay	2.1	
Gypsum, cement, asphalt workers (Switzerland)		Calcium sulphate, silicates, etc.	1.9	
Slate quarrying (Wales)	A small amount	Chiefly aluminium silicate	1.8	15.4
Stripping and grinding cotton carding machines		Husk of cotton and débris	1.7	12.8
Limestone masons (Derbyshire)	About 1 per cent	Calcium carbonate	1.7	12.0
Limestone masons (England and Wales)	About 1 per cent	Calcium carbonate	1.6	9.8
Limestone masons (Isle of Portland)	About 1 per cent	Calcium carbonate	1.4	
Ironstone mining		Ironstone and limestone	1.5	13.7
Millers (England and Wales)		Carbohydrate	1.4	9.1
Manufacture of plaster and cement (England and Wales)		Various silicates	1.2	11.6
Coal-mining		Carbon	1.0	9.8

Note: Compiled from various sources:

(1) All industries which involve exposure to appreciable amounts of silica in the dust have death-rates from phthisis above the standard used, e.g., occupied and retired males.

(2) The order arranged according to mortality bears a close relation to the amount of silica present in the dusts. The exceptions are caused by the exposure being more intense in some cases than in others, e.g., the pneumatic tool of the granite cutter raises more dust than the chisel and mallet of the stonemason.

Intelligent interest and cooperation of operators, such as has been shown by the large works in Vermont, point the way very definitely to better prophylaxis and treatment in this malady.

Reduction of amount of dust

1. Use of respirators. Respirators have been many and varied. The ancients, as recorded by Pliny (157), used bladders over their faces when they worked in vermilion. Linen cloths over the mouths of workers while in the dust have been recommended by numerous authors. The use of a gauze helmet for needle grinders was recommended by Johnstone (97) in 1799. Thackrah (202) observed in 1831 that machine workers who used grindstones covered their faces with handkerchiefs. An ingenious respirator was devised by Abraham and described by Holland (91) in 1843. It was designed with the idea of arresting metal particles which were thought to be the source of danger in the dust from grinding machines. It consisted of a guard or mouthpiece with a radial arrangement of magnets about the mouth which should deflect particles of iron and other metals from the path of the inhaled air. Holland noted that it doubtless did some good but had a very limited application because (1) only a small proportion of workers would wear it and especially because (2) it did not prevent the inhalation of gritty, nonmetallic particles which do great harm.

Simple respirators or face masks for protection against dust have been recently recommended by the New York Department of Labor (142), by Dunlap (52) and by Lockhart (116). Yet, as Böhme (17) recently pointed out, no respirator so far devised has been adequate in removing a sufficient amount of the finer dust particles to insure freedom from pneumonoconiosis by its use; and this for the reason that masks made with a mesh small enough to prevent permeation by the most minute particles render respiration difficult. Therefore, respirators offer but a partial solution. They should be used more extensively than is the case at present but their use should be combined with other methods of protection.

2. "Wet" methods. Reduction of the amount of fine dust in the air which workers must breathe is of far greater importance than the use of respirators, valuable as the latter may be in certain circumstances. This may be done both by lessening the production of dust and by removal of generated dust. In the production of dust, drilling (in mines) and grinding (in manufacturing industry) lead the field, and both were formerly carried on in the dry state. Many of the early writers noted a difference in the incidence and degree of disease amongst dry and wet grinders. Thackrah (202) for instance reported (1831) that the Sheffield "fork grinders, who use a *dry* grindstone, die at the age of 19 to 32, while the table knife grinders, who work on *wet* stones, survive to between 40 and 50." Holland (91) commented on the proposition in like vein in 1843. In the ordinary wet grinding process the wet dust is washed out onto the floor or nearby surroundings. If this is allowed to dry, then there are a large number of particles which may be disengaged by walking, or jarring, so that potentially at least wet methods offer a considerable menace—much more than an adequately ventilated dry work place does, according to Winslow and Greenburg (233).

Bolles (18), writing in 1881 on the industrial history of the United States, stated that in the grinding rooms of ax factories, "the fine dust flies in clouds from the stones in every direction, notwithstanding the stones are all the time completely deluged with water." Winslow and Greenburg (233), from whose article this quotation is taken, stated that, contrary to the prevailing opinion (Oliver (145), Lush (118), Lloyd (115), Price (161), Thompson (204)) "the protection afforded by wet grinding, as compared with dry grinding, is illusory." They found that the atmosphere in dry grinding sheds (with exhaust system) often contained less than one-tenth the number of dust particles that were found in surroundings of the wet grinding process. They attributed this to two facts: namely; (1) The grinders, doing piece work, find that a wet stone slows up production and they prefer to work with a moist rather than a wet stone; and (2) the absence of any exhaust system in the wet shops.

However, the general trend of opinion has been that wet processes, properly employed, contribute very materially to lessening the quantity of dust in inhaled air. The machine drills so equipped that a spurt of water is delivered during drilling through perforations in the bit are extensively employed and in several mining communities are required. According to Harrington (79) it is at first difficult to beat down the miners' opposition to the drill, but once they are shown the advantage of the "wet" tool, they almost invariably insist upon the latter.

External sprays have also been used for dust-laying but without great success.

Wet drilling and grinding are associated with wet clothing, high humidity, (especially in mines), and, in the opinion of the workers and some physicians, an increased liability to colds, and arthritis. Also it is to be remembered that wet drilling does not affect the fine dust which originates from blasting and which is inevitably suspended in mine air. This fine, suspended dust should be treated as a gas (Haldane) and should be dealt with by ventilation and exhaust systems. Moisture in the air facilitates inhalation of the particles which remain. It also tends to protect tubercle bacilli from the deleterious effects of drying.

3. "Dry" methods. Of the methods devised for reducing the amount of dust in the air none has been so efficacious as ventilation combined with suction and exhaust systems. These are employed in shops, especially where "dry" methods are in vogue but are not used extensively in mines as yet. Modern ventilating and suction systems are required by ordinance in many localities in the dusty industries and, to a lesser extent, in mines. After a review of the numerous ways of removing dust, Allen (4) has come to the conclusion that drawing it into a conduit by an inflowing suction is far superior to any other scheme of removal. It is interesting that nearly one hundred years ago Holland (91) devised a simple suction apparatus consisting of a wooden funnel, pipe and fan which removed a great deal of dust in grinding shops. Agricola (1) advocated ventilation of mines.

4. Blasting. Blasting creates the finest of dust particles and produces them in the largest numbers. Nearly all of the particles are below 12 microns and the average particle is 2.5 microns. The air after blasting is charged with these fine particles which have been found to number as many as 86,000 million (500 mgm.) to the cubic meter. This dust penetrates the atmosphere over large areas. Unless removed by ventilation it may be suspended easily in the air by operations in the mine, subsequent blasting, etc., even after it settles. Lack of strict control of blasting has in the past been a potent cause of silicosis. In the South African mines prescribed standards of ventilation regulate the frequency and type of blasting, which is allowed in a given mine but once in 24 hours.

5. Use of composition wheels. It has already been stated that carborundum and other composition wheels contain but little free silica. In addition to this, they are very hard and therefore wear longer and yield much less dust than do sandstone wheels. In Sheffield composition wheels have been substituted for sandstone (162). One such wheel three and one-half feet in diameter will last for 10 years while a sandstone wheel six feet in diameter will be worn down in less than six months. Thus, even if the percentage of silica were the same, the sandstone wheel generates 100 times as much dust as the composition one does. Macklin and Middleton (123) investigated this question in England by examining 1,153 grinders, among whom there were 53 cases of tuberculosis. Of these 7.07 per cent were wet sandstone *hand* grinders and 2.76 per cent represented all other types of grinder (wet sandstone machine, dry sandstone grinders, cutters, grinders using composition wheels, glazers and dressers). The advantage to the workmen of such a scheme as this is so clear as to call for little comment.

6. Standardization of dustiness. Another measure in prevention and one closely related to the various "wet" and "dry" processes is the standardization of the dustiness of the atmosphere which workmen must breathe. As a result of long experience, officials of the mines on the Rand came to require that mine air shall contain not more than five milligrams of dust to the cubic meter. In many work places, however, where dry processes are used and poor ventilation prevails the amount may be more than 500 mgm. to the cubic meter of air. Higgins, Lanza, Laney and Rice (85) have suggested as a standard a concentration of less than one milligram per 100 liters of air. Such a concentration, they held, is ordinarily safe; one above that is ordinarily unsafe. But in the Final Report of the Miners' Phthisis Prevention Committee (55) some interesting data are given in a discussion of the relation between weight and number of dust particles. It is contended that a milligram of particles measuring two microns in diameter will contain many more particles than would the same weight of particles having a diameter of 6 or of 10 microns. This report stated that in air containing five milligrams of dust per cubic meter the number of particles may vary from 85 to 700 per cubic centimeter when the average diameter of the particles is not greater than 5.4 microns.

It also showed that the number of particles per milligram may vary from 17 to 140 million. So it is clear from this that the standardization which is based solely upon weight is unsound in principle and unsafe in practice and that the gravimetric method is not as dependable as the counting method. Gravimetric methods fall down in furnishing a true index of the hazard particularly when the individual particles are large (and heavy). The standard count which is within the limits of safety (55) is 300 particles or less per cubic centimeter as will be seen from the statement given below, which is taken from this report.[18]

There follows this report, however, a minority report which brought into serious question this particular method of determination of dust content in the air and left the whole question in a rather uncertain state.

The counts on a given sample of air vary a good deal depending upon the type of apparatus used. The above estimations were made with the Kotze-Konimeter. Greenburg (70), in a comparative study of the several accepted methods, has shown that the konometer has many points in its favor and several objections. It takes an instantaneous sample; it does not allow gravimetric analysis and it yields low results when the air is heavily charged with dust. Apparently the impinger method yields the best results.

7. *Summary of "wet" and "dry" methods.* The following quotation from the last report (1928) of the Miners' Phthisis Medical Bureau (175) is germane, for in terse, summary fashion it presents very briefly the prevailing conception in South Africa of these preventive measures:

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[18] "In this connection it is of interest to compare the number of particles inhaled with the number actually found in the lungs. A recent estimation of the dust in the lungs of a person who had died with phthisis shows that they contain about 13 grams of silicious dust, consisting of 20 million million particles. If a man at work breathes one cubic foot of air per minute containing 300 particles per cubic centimeter, and if they were assumed to be all silicious, and if he works 300 days of eight hours each in the year, it would take him 16 years to inhale the 13 grams mentioned. Since the lungs are normally capable of dealing with some of the dust entering them, and since all the dust in the air does not reach the lungs, it is obvious that the period is much longer than 16 years.

"If, therefore, a standard of 300 particles per cubic centimeter be adopted as the upper limit of safe working, the probability is that, under ordinary circumstances, the conditions will be such as to approximate to an amount of dust represented by half this number."

"Although the use of water has contributed very largely to the great reduction of the dust content of mine air which has been brought about and which has completely altered the general picture underground, nevertheless, experience on the Rand has shown that the use of water as a preventive of 'miners' phthisis' not only has definite limitations, but has certain positive disadvantages. It will take one a large part of the way, but it will not take one all the way."

These limitations and disadvantages are fairly numerous. Water is remarkably efficacious in laying coarser dust at its source in both mine and shop, but it is not equally efficacious in removing the very finest particles, particularly the particles formed by blasting. Even with most complete spraying systems, there remains in mine air, after blasting, a residuum of very fine dust which is susceptible to removal only by ventilation. It should be treated as a gas (Haldane). A humid air affords a much better vehicle than does a dry air for the inhalation of dust. It also facilitates the intake of tubercle bacilli which may be suspended in the air. The latter circumstance, however, occurs much less commonly in wet than in dry surroundings. Pathological investigations have led to the general belief among South African workers that tuberculous infection is most commonly conveyed by inhalation of a contaminated atmosphere. Dry methods should be developed further. Further, at the depths and the temperatures at which mining is now being carried on, an increase in the humidity of mine air tends, by preventing loss of heat from the body, markedly to diminish working efficiency, and may in individual cases lead to serious results from a rise of the body temperature.

Physical examination of employees

1. Initial and periodical examinations. No scheme of prophylaxis could be adequate which did not contemplate the physical status of workers both at the beginning of employment and at periodic intervals during the latter. Such examinations should look into the condition of the upper respiratory tract to ascertain anatomical faults, for, as already indicated, people with abnormalities of this tract are definitely prone to early development of pneumonoconiosis. These examinations should be made with especial regard to the existence of tuberculosis, past or present, or of other diseases of the lungs, or of evidence of faulty respiratory function. Unusual limitation of pulmonary expansion, abnormal shape or marked asymmetry of the chest should eliminate the applicant. It is obvious that gross defects in the upper respiratory tract ought automatically to rule the applicant out of dusty work. The presence of any sign of tuberculosis—active or inactive—in the lungs or any other part of the body is almost always regarded as an absolute contraindication to employment in siliceous dusts. In South Africa any disease of the lungs eliminates the prospective worker from underground employment although such persons may obtain work above ground. The so-called vertical or "drop" heart is also a contraindication to employment within the mines because it is one of the signs most commonly encountered in tuberculosis (173). This sign, however, probably represents nothing more than a state of asthenia which may be brought about by a good many other causes than tuberculosis. Tuberculosis is by far the most common cause of invalidism in people with pneumonoconiosis, and its introduction should be prevented in every possible way. It is obvious that the physical examination would take into account cardiac and other disabilities of the applicant.

Periodical examinations of workers after employment has been obtained are of quite as much importance as initial examinations, because pneumonoconiosis eventually develops in many men who are exposed sufficiently long to the inhalation of siliceous dusts. It is obvious that this affection should be detected in its earliest stages, for removal of the worker from the dust at the beginning of his affection will go far toward prolonging his life and continuing his productivity even though the disease tends to be progressive irrespective of further exposure. The silicotic person has a definitely increased susceptibility to tuberculosis which constitutes another valid and important reason for periodic examinations. The beginning silicotic should be removed in an effort to prevent him from developing tuberculosis. Too, periodic examinations will detect tuberculosis in its beginning stages and, by leading to removal of the affected workmen, will both give him an opportunity for early treatment and eliminate a new source from which tubercle bacilli may emanate and spread to fellow workmen.

Periodical examinations were made on 14,726 persons in the South

African mines last year (175). Of these, 427 were found to have simple silicosis and gave a "prevalence" rate of 2,899 per 100,000. Of these 427, however, 144 had been detected in previous examinations but had remained at work. These deducted, there remained 283 "new" cases which gave a "production" rate of 1,941 per 100,000, as compared with a rate of 2,691 for 1926–1927 and one of 3,859 per 100,000 for 1925–1926. It is a fact of especial significance that of these 283 "new" cases of silicosis only 19 had at any time ever passed the initial examination. It is an equally important fact that, of all new miners who had passed the initial examination and who had never been previously employed in mining occupations, only 30 have developed silicosis, and the examinations were instituted in 1916. Such data, without further comment, make an excellent case for the initial physical examination.

In these mines no new miner is given employment now unless he have an "initial certificate" which states that its holder "is free from any disease of the lungs and respiratory organs, and is in other respects physically fit for underground work." The holder keeps this certificate for six months of employment when he is entitled to appear for a "periodical" examination. The purpose of the initial examination is to debar all persons who appear more susceptible than the average to either tuberculosis or pneumonoconiosis. It is a very rigorous one and results in a rejection of one-third to one-half of the applicants.

During the year from July, 1927 to July, 1928, no new cases of tuberculosis with silicosis developed among the nearly 15,000 Europeans (miners) in South Africa.

Pneumonoconiotics are peculiarly susceptible to tuberculosis. This fact makes it plain that *prompt elimination of tuberculous individuals from shops and mines* is the only sensible course to pursue, once the case is detected. It is obviously the most important single prophylactic measure.

To follow the reports of the Miners' Phthisis Medical Bureau from year to year for the last ten years is to realize graphically how gratifying has been the progress in markedly reducing the incidence of silicosis and of tuberculosis with silicosis. But such a perusal reveals the fact, commented on elsewhere, that the amount of simple tuberculosis as such has not declined appreciably and in certain years has actually appreciably increased.

2. Roentgenological examination. No examination, initial or periodic, should be considered as adequate or complete unless an x-ray of the chest be included. No single feature is so important in indicating early stages of pneumonoconiosis, tuberculosis, or the two diseases in combination. This subject had been considered under the heading of Diagnosis.

3. Sputum examination. No small part of the examination, particularly the periodic examination, is study of the sputum. *Routine and careful, repeated search of the sputum for tubercle bacilli is imperative in every worker in dusty trades who has cough and expectoration.* Last year the Miners' Phthisis Medical Bureau examined 23,426 specimens of sputum of which 2,388 were from Europeans and the remainder from natives. Among the former, tubercle bacilli were found in 305 instances or 12.77 per cent and among the latter they were present in 3,615 instances or 17.18 per cent (175). This number of sputum examinations gives some indication of the importance attached to the procedure on the Rand.

General hygiene

The significance of this heading is obvious. Its implications have appeared several times in different sections of this treatise and they are so obvious as to require little further elaboration. It is one of the especially important considerations in the prevention of tuberculosis in people with pneumonoconiosis.

Disinfection of work places has had some vogue. This has been done usually by means of fine sprays of carbolic acid solution or of proprietary products having this substance or its derivatives as the chief germicidal reagent. In the South African mines disinfection has been practiced a good deal. It apparently has some advantages. It is interesting in this connection to note that tubercle bacilli have been found capable of setting up tuberculosis even after they had been left for two months in acid mine water (55).

Compensation

No scheme of treatment is adequate or complete which does not include compensation to employees who are rendered unfit for work by this disease, for the latter is purely an occupational disease for which compensation should be awarded. The best and most carefully worked out scheme of this sort is that in force now in the gold mines of the Rand. In this region the three diseases for which compensation is specified by legal regulations are simple silicosis, tuberculosis with silicosis and simple tuberculosis. The conditions under which compensation is granted are given in the following statement which is taken from one of the recent reports (175):

> By "Simple Silicosis" is meant silicosis without a definitely recognizable or 'overt' tuberculosis; by "Tuberculosis with Silicosis" is meant silicosis with overt tuberculosis; and by "Simple Tuberculosis" is meant tuberculosis of the respiratory organs, without detectable silicosis.
>
> Any working miner who is found to be suffering from one or other of these conditions is notified to that effect. If he is found to have tuberculosis with silicosis, or simple tuberculosis, he is obliged to relinquish underground work immediately. If he is found to have simple silicosis, it is optional for him to take an award and leave underground work, or to remain at work and postpone taking an award. Should the miner, however, remain at work under ground for a period longer than three months after receipt of a notification that he has silicosis, he forfeits during his lifetime all right to an award other than that to which he would have been entitled at the date of his first notification.

The Bureau is the usual arbiter, but there is also a Medical Board of Appeal which must occasionally decide upon an award. This scheme has apparently worked very satisfactorily, and it or a modification of it is in use in certain other countries. It is to be recommended.

Other prophylactic measures

In addition to careful physical examination and the other preventive measures already discussed, the following recommendations have been suggested (Middleton (128)):

1. Avoidance of closed shops. Masons and others should carry on their work in the out-of-doors as much as possible.

2. Replacement of sandstone wheels by composition wheels which give off much less silica, both because they are much harder and because they contain much smaller proportion of uncombined, crystalline silica.

3. Coöperation of workmen. The potential dangers inherent in the particular occupation should be explained; prejudice and suspicion between employer and employee should be done away with as much as possible.

4. Legal regulations requiring prescribed floor space for workmen and distance between them. Koelsch (106) has stated that in Germany employees handling or using sandstone must work at least two meters apart in rooms that are at least three meters high; each worker must have two square meters of floor space and ten cubic meters of air space, the latter increased to 50 cubic meters if the place is smoky or unusually dusty.

Recapitulation of prophylaxis

There should be put forth a decided effort to prevent the occurrence of pneumonoconiosis and its complications by the use of both mechanical and medical precautions such as (1) prohibition of dry drilling, (2) prohibition of dry or wet grinding without adequate suction for removal of dust, (3) institution of initial and periodical physical examinations and all that appertains to these in the way of removal of ill or potentially ill employees from occupation, treatment and compensation of such workmen. All these measures have justified themselves abundantly wherever they have been properly employed and in no place more than in South Africa. In this country there has been a great improvement in the general standard of health, a reduction in incidence of pulmonary tuberculosis (among underground workmen) from 259 per 100,000 in the year 1917–1918 to 90 per 100,000 in the year 1923–1924 among European miners, and from 576 to 328 per 100,000 for the same period among native laborers. It seems reasonable to assign a considerable part of this decline to the measures employed. Also simple silicosis appears in a less severe form; there is an increased prospect of survival among the cases, a lengthening of the period of employment before the appearance of symptoms and a decrease in the number of lesions found in autopsy.

In the diseases under consideration, especially pneumonoconiosis, prophylaxis is vastly more important than treatment, although treatment avails a good deal in a palliative way. Despite the fact that silicosis progresses irrespective of change to a nondusty environment, removal of the miner usually follows. In the experience of numerous writers, early stages of pneumonoconiosis may become arrested by removal to a rural, nondusty atmosphere. Such is the recommendation of the New York State Department of Labor (McBirney (119)). Likewise in Australia reports (Smith (195)) state that the subsequent development of tuberculosis in pneumonoconiotic individuals thus removed from work is very much less common than in those who, although retired from work, remain in the locality as before. Smith attributed much of this, however, to contact with the tubercle bacillus in more densely settled, civilized communities. It stands to reason that the progress of the affection might be somewhat mitigated and its rate slowed by removal of the irritant which has induced the disease, although it does tend to be progressive. In this connection Oliver has quoted Aitken who wrote as superintendent of Modderfontein Sanatorium in South Africa, that in his belief the fibrous tissue in pneumonoconiotic lungs undergoes partial absorption in persons removed from dusty atmospheres provided they are free from tuberculosis and their hearts can withstand the long strain that is inevitable in marked degrees of pneumonoconiosis.

People with pneumonoconiosis to which tuberculosis has been superadded require to be kept on a tuberculosis regimen such as that maintained by any well-ordered sanatorium. Such patients should be given the advantages of sanatorium treatment for an extended time, because their tuberculosis may run a more chronic course than does the ordinary uncomplicated case of tuberculosis. They should have such treatment as a right because pneumonoconiosis should be a compensable disease everywhere.

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